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TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS.

TWELFTH SESSION,

HELD AT WASHINGTON, D. C.,

MAY 4, 5, AND 6, 1897.

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M. ALLEN STARR, M.D.

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(FROM ITS ORGANIZATION TO THE PRESENT TIME.)

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1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.

MEMBERS.

* Original Members.

ELECTED

1892. ABBOTT, ALEXANDER C., M.D., Laboratory of Hygiene, University of Pennsylvania, Philadelphia.
1896. ABEL, JOHN J., M.D., 1604 Bolton St., Baltimore.
1894. ADAMI, J. GEORGE, M.D., Pathological Laboratory, McGill University, Montreal, Canada.
*1886. ADAMS, J. F. A., M.D., 26 Wendell Ave., Pittsfield, Mass.
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*1886. BAUMGARTEN, G., M.D., 2643 Chestnut St., St. Louis.
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1895. BILLINGS, FRANK, M.D., 235 State St., Chicago.
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*1886. BUSEY, SAMUEL C., M.D., 1545 I St. (N. W.), Washington, D. C.
1889. CARY, CHARLES, M.D., 340 Delaware Ave., Buffalo, N. Y.
*1886. COUNCILMAN, WILLIAM T., M.D., Harvard Medical School, Boston.
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*1886. DANA, ISRAEL T., M.D., 181 State St., Portland, Maine.
1888. DANFORTH, I. N., M.D., 903 W. Monroe St., Chicago.
*1886. DELAFIELD, FRANCIS, M.D., 12 W. 32d St., New York.

ELECTED

1893. Dock, George, M.D., University of Michigan, Ann Arbor, Mich.
*1886. Draper, William H., M.D., 19 E. 47th St., New York.
*1886. Edes, Robert T., M.D., Adams Nervine Asylum, Jamaica Plain, Mass.
1888. Ernst, Harold C., M.D., 8 Greenough Ave., Jamaica Plain, Mass.
1890. Fisk, Samuel A., M.D., 37 18th Ave., Denver, Col.
*1886. Fitz, Reginald H., M.D., 18 Arlington St., Boston.
1895. Fischel, W. E., M.D., 2647 Washington Ave., St. Louis.
1895. Flexner, Simon, M.D., Johns Hopkins Hospital, Baltimore.
*1886. Folsom, Charles F., M.D., 15 Marlborough St., Boston.
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1890. Griffith, J. P. Crozer, M.D., 123 S. 18th, St., Philada.
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ELECTED

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*1886. TYSON, JAMES, M.D., 1506 Spruce St., Philadelphia.
1895. VAN GIESON, IRA T., M.D., 1 Madison Ave., New York.
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1889. WALCOTT, HENRY P., M.D., 11 Waterhouse St., Cambridge, Mass.
*1886. WARD, SAMUEL B., M.D., 281 State St., Albany, N. Y.
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1894. WILLIAMS, FRANCIS H., M.D., 505 Beacon St., Boston.
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*1886. WOOD, HORATIO C., M.D., 1925 Chestnut St., Philadelphia.

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ASSOCIATION

OF

AMERICAN PHYSICIANS.

CONSTITUTION

AS AMENDED MAY 4, 1897.

ARTICLE I.

Object and Name.

This Association has for its object the advancement of scientific and practical medicine, and shall be known as THE ASSOCIATION OF AMERICAN PHYSICIANS.

ARTICLE II.

Members.

The number of active members shall be limited to one hundred and twenty-five. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

ARTICLE III.

Officers.

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually;

five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

Article IV.

Duty of Officers.

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of Transactions.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

Article V.

Council.

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

Article VI.

Meetings.

1. The Association shall hold an annual meeting in the City of Washington, D. C., at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. Authors of papers, and referees and co-referees who open a discussion shall not occupy more than thirty minutes each; and in the discussion following, the remarks of each speaker shall be limited to ten minutes.

5. The referees, co-referees, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

Article VII.

Quorum.

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum; and for altering the Constitution, twenty-five members shall be necessary.

Article VIII.

Election of Members.

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee, and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

Article IX.

Annual Dues.

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

Article X.

Amendments to the Constitution.

Amendments to the Constitution must be proposed in writing by five members at an annual meeting and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendments; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

TWELFTH ANNUAL MEETING,

Held in Washington, D. C., May 4, 5, and 6, 1897.

The following members were present during the meeting:

A. C. Abbott.
J. J. Abel.
J. G. Adami.
J. F. A. Adams.
I. Adler.
I. E. Atkinson.
A. B. Ball.
H. M. Biggs.
F. Billings.
N. Bridge.
S. C. Busey.
C. Cary.
W. T. Councilman.
E. G. Cutler.
J. M. Da Costa.
C. L. Dana.
F. Delafield.
G. Dock.
William H. Draper.
R. T. Edes.
S. A. Fisk.
R. H. Fitz.
S. Flexner.
M. H. Fussell.
J. P. Crozer Griffith.
J. Guitéras.
H. A. Hare.
I. M. Hays.
H. Hun.
H. M. Hurd.
A. Jacobi.
E. G. Janeway.
W. W. Johnston.
F. P. Kinnicutt.
H. A. Lafleur.
A. McPhedran.
A. L. Mason.
S. J. Meltzer.
J. H. Musser.
W. P. Northrup.
William Osler.
G. L. Peabody.
D. W. Prentiss.
T. M. Prudden.
H. C. Wood.
J. J. Putnam.
B. K. Rachford.
W. Reed.
B. Robinson.
T. Rotch.
F. C. Shattuck.
G. B. Shattuck.
W. Sinkler.
A. A. Smith.
L. Starr.
M. A. Starr.
G. M. Sternberg.
D. D. Stewart.
James Stewart.
C. G. Stockton.
W. G. Thompson.
J. Tyson.
W. H. Welch.
J. T. Whittaker.
G. Wilkins.
F. H. Williams.
J. C. Wilson.

Tuesday, May 4th.

The President, Dr. J. M. Da Costa, called the Association to order at 10 A.M., and delivered

The President's Address.

(See page 1.)

At the conclusion of his Address he said:

Allow me a few words as regards our Association and the meeting that is before us. Fortunately, we have been spared the loss of any member by death. The proposition to increase the membership is again before you for action. It is well known that many doubt its wisdom. There are but few vacancies and a long list of candidates for them, making choice very difficult. The question I ask to present to you is whether we could not make a freer use of our honorary list, and transfer to it those who have been members for a long time but find it inconvenient to attend with regularity, yet wish to remain with us? By doing so there would be a larger number of vacancies on our active list. The very extensive number of papers on the programme shows the life of the Association and the keen interest of its members, while it bespeaks a session that we all trust will be memorable for common instruction and for general good.

The Secretary announced the names of the officers and candidates for membership recommended by the Council for election, and that the Council favored the adoption of the amendment to the Constitution, introduced at the last annual meeting, increasing the active membership to one hundred and twenty-five.

Dr. Busey moved that this amendment to the Constitution be adopted, and, after a discussion participated in by Drs. Griffith, Mason, Hun, Jacobi, Tyson, Osler, and G. B. Shattuck, this motion was passed.

The Treasurer then made his annual report, which was referred to an auditing committee, consisting of Drs. Atkinson and Sternberg.

Dr. Busey then presented a communication requesting the Association to petition the President and Vice-President of the United States, the Secretary of the Navy, the Speaker of the House of Representatives, and the Naval Committees of both Houses of Congress to enact such legislation as shall confer upon the officers of the Medical Corps of the Navy the same definite and positive rank, rights, and military status as are now, and have been for many years, accorded to the medical officers of the Army.

On motion of Dr. Sternberg, this communication was referred to the Council for verification and advice.

Dr. G. B. Shattuck then read a paper entitled "The Serum Test in Typhoid Fever," which was discussed by Drs. Abbott, Musser, Osler, Biggs, Atkinson, Tyson, Billings, Whittaker, F. C. Shattuck, and Janeway.

Dr. A. L. Mason then read a paper entitled "Gall-bladder Infection in Typhoid Fever," and Dr. Osler read a paper entitled "The Hepatic Complications of Typhoid Tever," and both papers were discussed by Dr. Councilman.

Dr. Tyson then read a paper entitled "Urea Estimations in Cases of Typhoid Fever Treated by the Brand Bath Method."

Dr. Dock read a paper entitled "Cancer of the Stomach in Early Life, and the Value of Cells in Effusions in the Diagnosis of Cancer of the Serous Membranes," which was discussed by Dr. Flexner.

Dr. Delafield read a paper entitled "The Inflammations of the Colon."

Dr. Prentiss, instead of reading his paper, exhibited "Two Cases of Erythromelalgia" (Mitchell).

The Association adjourned at 1.20 P.M.

WEDNESDAY, MAY 5TH.

The President, Dr. Da Costa, called the Association to order at 10.10 o'clock.

On motion of Dr. Musser, it was resolved that the session of May 6th commence at 9 A.M.

Dr. McPhedran read a paper entitled "A Case of Pancreatitis followed by the Formation of a Cyst."

Dr. Musser read a paper entitled "Angina Pectoris; its Relation to Dilatation of the Heart," which was discussed by Drs. Sinkler, Wood, Janeway, Cary, Musser, and Kinnicutt.

Dr. F. C. Shattuck read a paper entitled "Pericarditis; Some Points in its Diagnosis and Treatment," which was discussed by Drs. Whittaker, Peabody, Hare, Rotch, Bridge, Tyson, McPhedran, Williams, Janeway, and Shattuck.

Dr. Robinson read a paper entitled "Diagnostic and Therapeutic Considerations with Respect to Certain Affections of the Upper Air-tract."

Dr. Wilson read a paper entitled "Nervous Deafness in Diphtheria," which was discussed by Drs. Robinson, Atkinson, Fussell, Johnston, and Wilson.

Dr. Griffith exhibited the specimens illustrating his paper on "Types of Œdema in Infancy."

Dr. D. D. Stewart read a paper entitled "A Further Communication on the Occurrence of a Hitherto Undescribed Form of Chronic Nephritis Unassociated with Albuminuria."

Dr. Hare then read a paper entitled "A Study Concerning the Cumulative Action of Digitalis," which was discussed by Drs. Osler, Janeway, Wilkins, Wilson, Whittaker, Cary, McPhedran, Hare, and Williams.

Adjourned at 1.30 P.M.

MAY 6TH.

The President, Dr. Da Costa, called the Association to order at 9.05 A.M.

Dr. Edes read a paper entitled "The Relation of Neurasthenic Conditions to the General Nutrition with Reference to (*a*) Body-weight (*b*) Blood-measurement (*c*) Excretion of Urea, Uric Acid, and Indican," which was discussed by Dr. Putnam.

Dr. Bridge read a paper entitled "The Reflex Neuroses of the Abdomen," which was discussed by Drs. Welch and Stockton.

Dr. Williams read a paper entitled "The Röntgen Rays in Thoracic Diseases," which was discussed by Dr. Fitz.

Dr. Osborn, of New Haven, was introduced by Dr. Welch, and demonstrated specimens taken from a case of acromegaly.

The Association passed a vote of thanks to Dr. Osborn for his interesting and valuable demonstration.

Dr. Abel read a paper entitled "The Chemical Properties of the Blood-pressure-raising Constituent of the Suprarenal Capsule," which was discussed by Dr. Osler.

Dr. Flexner read a paper "On the Occurrence of the Fat-splitting Ferment in Peritoneal Fat-Necrosis," which was discussed by Dr. Welch.

Dr. Abbott read a paper entitled "Further Studies upon the Pathogenic Spirilla of the Schuylkill River at Philadelphia," which was discussed by Dr. Sternberg.

Dr. Reed read a paper "On the Appearance of Certain Amœba-like Bodies in the Blood of Vaccinated Monkeys (Rhœsus) and Children and in the Blood of Variola."

Dr. Williams presented a clinical, and Dr. Councilman a pathological, report "On an Epidemic of Cerebro-spinal Meningitis caused by Diplo-

coccus Intracellularis Meningitidis" (Jaeger), which were discussed by Drs. Guitéras, Williams, Councilman, and F. C. Shattuck.

Dr. A. A. Smith reported "A Case of Levant Fever," which was discussed by Drs. F. C. Shattuck and Dock.

Dr. Whittaker read a paper entitled "Note on the Earliest Possible Recognition of Tuberculosis," which was discussed by Drs. F. C. Shattuck and Mason.

Dr. de Schweinitz read by invitation a paper entitled "Antitoxic Serum for Tuberculosis."

Dr. Hare read a paper entitled "A Further Study of some of the Untoward Effects of the Bromides," which was discussed by Drs. Wood, Atkinson, and Hare.

During the meeting the following papers were read by title:

"Analysis of 3000 Cases of Melancholia," by Dr. S. Weir Mitchell.

"A Case of Acute Ascending Paralysis; Recovery," by Dr. A. McPhedran.

"Pneumonia in Private Practice," by Dr. J. H. Fussell.

"Clinical Notes of a Case of Broncho-biliary Fistula," by Dr. J. E. Graham.

"The Effects of Various Metals and Metallic Salts on the Growth of Certain Bacteria," by Drs. Bolton and Brown.

"On a Case of Adenoma of the Liver, with Complications," by Dr. A. Jacobi.

"Types of Œdema in Infancy," by J. P. Crozer Griffith.

"The Treatment of Lithæmia," by Dr. B. K. Rachford.

"Primary Tuberculosis of the Kidney," by Dr. D. D. Stewart.

The Committee appointed to audit the Treasurer's accounts reported that they had examined the accounts and found them to be correct. Their report was accepted and the Committee discharged.

It was resolved that the thanks of the Association be returned to the President and Faculty of the Columbian University for their courtesy in furnishing the Association with a place of meeting.

The Council made a report on the petition, referred to it by the Association, in regard to the ranking of the Medical Officers in the United State Navy as follows: that the Council considers that the verification of this complaint and petition, as directed by the Association, is beyond its power, and feels indisposed to advise the Association to take action in the matter. This report was accepted and adopted.

The Association then proceeded to the election of Officers, and the following were unanimously elected:

President —F. C. Shattuck.
Vice-President.—G. Baumgarten.
Recorder.—I. Minis Hays.
Secretary.—Henry Hun.
Treasurer.—W. W. Johnston.
Councillor.—M. A. Starr.

The following elections to membership were made on the recommendation of Council.

Honorary Members.—Samuel C. Chew and F. T. Miles, of Baltimore.

Members.—Arthur C. Cushny, of Ann Arbor; W. S. Thayer, of Baltimore; Ludwig Hektoen, of Chicago.

On motion of Dr. Sternberg, the thanks of the Association were tendered to Dr. Da Costa for the courteous and efficient manner in which he had conducted the meetings of the Association, and for the valuable scientific papers which through his exertions had been presented to the Association.

Adjourned at 1.30 P.M.

HENRY HUN,
Secretary.

PAPERS.

NOTICE.

THE Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

THE PRESIDENT'S ADDRESS.

TENDENCIES IN MEDICINE.

By J. M. DA COSTA, M.D., LL.D.

It is expected of the President of your Association that he offer some remarks as introductory to the scientific papers that are to occupy your attention, and every presiding officer has done so, expressing himself on subjects for some time in his mind or to which he has been recently giving heed. Thus, diversified and excellent addresses have been made, some treating of medicine and its aims in a broad, philosophical spirit; some reviewing its achievements; others giving most erudite and valuable historical information. In my turn I ask that you will indulge me if I present a few thoughts on what seem to me in our science the best tendencies of the day, as well as on certain causes that, with all the wonderful work being done, and with the immense energy and industry of the devoted laborers in four continents, retard its still broader and steadier development.

The greatest advance of our time—it seems trite to mention it to such an assembly—is the ardent study of the causation of disease. Students have speculated in all ages on the causes of disease; but these have been, for the most part, half-hearted speculations, made so by the feeling of impossibility of reaching a conclusion, or dogmatic assertions that, believed in for a time, soon became of interest only to the curious searchers for fragments on the shelving beach of science. Now, the recognition of minute organisms, their study, their artificial culture and modes of growth, their secretions, their chemical characters, their likes, their antagonisms, have let us into the secrets of another world and are showing us the way in which

infective maladies originate and the laws they obey. We are looking for infection in every disease; we are often keenly pursuing it where it probably does not exist; at all events, not in the shape of bacteria, which in our day we accept as a term almost synonymous with infection. A sense of causation, formerly deficient, has been replaced by a most acute sense, and by a desire for unrelenting search. What is still greatly needed is, I think, an appreciation of how infection may light up slow processes and lead to structural complications, such as are found, for instance, in the exanthemata. We have also much to learn of bacteria that exist normally becoming abnormal in certain perverted conditions, either in manifold growth, as happens with the bacillus coli communis, or in character. What we consider the cause may thus be only the consequence of disease. The soil and its forces, too, are to be studied and critically examined.

But the power of this little, invisible world is mighty. It is told of Napoleon that he could never understand the fame of Cuvier. He spoke of him, with something like contempt, as only occupied with small things. Yet smaller things conquered even him, the great conqueror. It was the plague bacillus, not Sir Sidney Smith, that compelled him finally to leave Syria and give up his dream of subduing the East, like another Alexander.

Other than mere bacteriological work forms a most valuable part of the contribution of the laboratory to the investigation of disease, and in the last decade has placed this investigation on a much higher plane. The microscopical and chemical examinations of the secretions and excretions and of the blood have become our daily duty. The chemical examinations, which, dealing, as they may be made to do, with the constantly varying problems of life in disease, have been temporarily overshadowed by the ardor of bacteriological research, will, with widening fields, resume their former prominence. The time is indeed at hand in which, without the ready access to a laboratory manned by experts in all these lines, or the association with a trained laboratory assistant, no physician can do his patients, himself, or his science justice.

Closely connected with the laboratory investigation of disease, especially with its chemical investigation, is the study of the effects of the products generated by decomposition of albuminous matter, producing, when developed in the dead body, the substances known

as ptomaïnes, when in the living body, as leukomaïnes. The recognition of these agents, so frequently poisonous, is explaining many obscure processes, is leading to new and close scrutiny of others and to search after means of neutralizing their toxic influence. It is with pride that this Association can view the history of this branch of research, for the fruits it has yielded have been largely gathered by the efforts of some of its own members.

Another of the best results of the achievements of our time is seen in the effacement of the strict division between medicine and surgery, or rather in the recognition that there are no lines separating them, but lines becoming continuous, on which joint action proceeds. We see this in the whole clinical history of appendicitis and its progressive unfolding; the more the medical part is studied and rendered precise, the more exact become the indications for operation and the appreciation of the chances of this. The same may be said of abscess and of tubercle of the kidney; of the investigations of the character of effusions into pleural, or pericardial, or peritoneal cavity; and of many other well-known conditions that surgeons and physicians are now studying together. This new tendency is sure to counteract not only the excessive specialism of our day, but to give us once more broader physicians and surgeons, taking the keenest interest in each other's work.

One of the greatest improvements in our generation is in the much better appreciation and larger use of hygienic means, of systematic exercise, of baths, of regulated rest, of out-door life. Then, too, when medicines are given they are much more generally used singly, with a view to their direct effect, and not in excessive combination. Moreover, the substitution of extracts and of active principles for many of the nauseous drugs has taken away the terror and disgust with which medicines were regarded. It is, from a pharmaceutical point of view, at least, no longer a punishment to be ill. The satire of Molière is lost to the playgoers of our generation. The highly appreciated answer of the Bachelor of Medicine, when examined for his doctor's degree, that the remedies are always "Clysterium donare, postea seignare, ensuita purgare," would fall at present on totally unsympathetic ears; for now there are delightful capsules, and triturates, and pills of æsthetic colors—"dear little pink pills," as I have heard them called, though the dear little pills happened to contain

strychnine. And the boy of the period is not tempted to view an open window as the only means of getting rid of the hated bottle; he may, indeed, want to take too much of it, because, with all its potency, it is sweet and pleasant.

The tendency of our time is to endeavor to overcome disease, and not merely to observe and palliate its ravages. We are going back to the doctrines of our forefathers; abandoned for a time, because, with an expanding knowledge from the study of pathology, the means they possessed were found to be, for the most part, totally inadequate. Thus there was a period of nihilism and expectancy in therapeutics. But so-called rational expectancy is but a confession of impotency. Now, the tendency is once more aggressive. We are trying directly to choke or to subvert morbid action, and doing this partly through the old, transmitted remedies of former generations, but employed with a better understanding of their real qualities, partly by new agents furnished by chemistry and by constant research in other fields. Of the former, the freer and more scientific administration of digitalis may be taken as an illustration; and the use of mercury, though in a different manner, is infinitely more prevalent than it was some years ago. To bleeding, too, I, for one, believe that we shall return; only it will be not the mere abstraction of blood perverted by disease, but there will be, with this, immediate attempts at the reconstruction of the blood by supplying it with the proper saline fluid and other ingredients. In the second class, the bromides, chloral, the nitrites, and nitroglycerin are prominent, as is a whole group of antiseptic agents. Many of these—it is especially true of the nitrites—have come to us from the physiological laboratory. One of the most interesting attempts at radical therapeutics is the endeavor to counteract the bacteria of disease by substances that form in the body which neutralize their toxic products. This antitoxin treatment is brilliant and hopeful, and is being tried in many affections, pre-eminently in diphtheria, in tetanus, and in erysipelas. It cannot be said that as yet it has led to any great results, though the evidence is decidedly in its favor in diphtheria. It seems scarcely worth while to push it in erysipelas—at least in erysipelas that the physician sees—for the mortality in this is, under any treatment, but very slight. How valuable the antitoxins will prove as preventives remains also to be solved. More productive thus

far has been the use of attenuated virus, as, for instance, in Pasteur's treatment of hydrophobia; the influence in cholera, in yellow fever, in bubonic plague, is now under keen observation. The effects on tuberculosis must be taken thus far as the expression of hope rather than of fact. The success of thyroid extract in the treatment of myxœdema is leading to the close investigation of the active principles supplied by other ductless glands. The next decade will prove whether the X-rays, which are making such wonderful additions to diagnosis, will also have their therapeutic triumphs. In it, too, we may look for some striking developments of suggestion, not only as explaining mental and morbid processes—what more extraordinary and thought-starting, for instance, than the recently tested production of special cutaneous affections by it?—but as a harnessed therapeutic force. All this is in the line of present investigation; and there will be much disappointment and wasted labor in particular points, but it is not too sanguine to believe that there will be also a solid outcome which will immensely advance scientific medicine.

There are, with all these tendencies of our day that work for good, some which, whether growing out of them or whether the exaggeration of old hindrances, have to be, in the interest of true science, strenuously guarded against. One that is very evident is the tendency to immediate generalization. The discovery of every new bacterium is supposed to revolutionize instantly the science of medicine, and is announced with all the air of the unexpectedness of genius. Fortunately or unfortunately, one may be discovered every day, and a man may thus find himself with three hundred and sixty-five opinions on the tenets of his art in the course of the year; but this would not daunt the enthusiasm of the insatiate generalizer:

> "Ten thousand great ideas filled his mind,
> But with the clouds they fled, and left no trace behind."

Fixity of opinion in medicine is a virtue, if the mind remain open to proof and be in sympathy with advance; and it is this freshness of mind, joined to good judgment, through which is best estimated the true value of the many facts constantly discovered in an advancing science like ours. Clinical medicine, indeed, must continue to be the final court of appeal for the purposes of the practitioner of medicine. Before that court will come and be listened to with sympa-

thetic interest, as eloquent advocates, those who are presenting the claims of special studies. But these must be well supported and judged in their bearing on the whole before new laws are laid down. And we see that the more we investigate and the more we know the more will old questions assume different aspects, the more they will have to be retested; there is no finality—there can be none—in medicine. When the last word is spoken we shall have a perfect science; until then there must remain for us a certain amount of empiricism, especially in treatment.

There is no doubt that, considering the amount of work done and recorded, medicine—especially clinical medicine—would be much more advanced if the records were differently made, and were not so vague as they often are. What is more provoking than to see constantly such loose statements as this: "The examination was negative." Negative as to what? If applied to the action of an organ, as to what part of its action? If to secretions, to what part of their constituents? How much easier to say, even if it have been an incomplete examination, for what exactly they were investigated, and how much more certain to be of use for comparison in similar cases. Worse still is it with the records of treatment. This is an ever-recurring expression: "The usual treatment was employed." I saw this in a recent volume of *Transactions* with reference to the congestion of the lungs in typhoid fever. What is meant? Is there such a thing as a fixed treatment for it the world over? It might mean dry cups to some; ammonia, turpentine, digitalis, or yet different things to others. Then the utter absence of mention of doses makes it impossible to say whether any remedy was fully tested, or to compare its action when given in small or in large quantities. For very many purposes records, as published, are valueless; in truth, they impede progress, and a little care would make it otherwise.

Then there are records which, made even to the full limit of industrious exhaustion, are so badly and confusedly presented that they bury themselves from the start. A little more time spent on their expression might make them absolute and convincing. It would be, indeed, well if in all our professional literature there were something more of the learning of the scholar and the clearness of the literary artist; men who followed the master, Harvey, in other

points besides profound and productive research. A few more Watsons and Pagets, Trousseaus and Hyrtls would make knowledge easier to obtain, more constantly with us, forming much more a part of our daily life and application. It is true that if, in our science, we must choose between profound inquiry and its clear enunciation, we shall choose the former. It is a pity, and it is unnecessary, that there should be any occasion for a choice. The French, with their lucidness in scientific matters, set all other nations an example. The countrymen of Goethe, foremost in investigation, following his avowed contemptuous indifference to style, are the greatest sinners against clearness and vivid expression. They evidently believe in the reverse of the thought with which Johnson excused the inaccuracies in Goldsmith's *Animated Nature*, that, if he once began to make experiments, life would be too short for him to get his book written.

One more tendency of the day let me notice, which is not for good, and undoubtedly retards progress. It is the excessive publication of half-knowledge, of doubtful fact, and of loose inquiry. The propensity for authorship is an old disease, but it has assumed a development commensurate with the prodigious development of everything else in the age in which we live. It is harmless in journalism, less so in literature, but positively dangerous in science; for it fills this with immature or false observation, and takes the time of others to remove the obstructions placed in the stream of knowledge. With some, want of sufficient training leads to it and absence of inquiry into what has been already ascertained; in others, it proceeds from a girl-like genius that, in place of letter-writing, pours itself out in medical periodicals, fascinated by penning sentences full of pseudo-scientific commonplace. It is far from being a disease only of the untried or ignorant; famed workers, too, may succumb to it, listening, perhaps, to the entreaties of friendly and sleepless editors. Who knows that it is not, after all, a physiological function, giving full play to brain-centres in very rare use—centres situated in what Oliver Wendell Holmes has called the idiotic area of the brain.

But whatever the retarding influences, they are not to any extent checking the onward course of medicine. The numerous inquiries, the keen experimentation and close research, the general thought-

fulness, are developing a resistless scientific method; resistless because it is true. Medicine is no longer an art founded only upon empirical observation, no longer a purely deductive science; it is becoming also an inductive one. The great body of the community is touched with friendly interest in watching its growth. With the advance of the scientific method special systems are crumbling; future ones are impossible. There can be no more pathies; the general intelligence will prevent it; for educated men are recognizing the broad base on which medicine is resting, and that truth is sought in it by the same means that are used in physics and in the highest development of other sciences. In our midst with all this, conviction is becoming clearer, purpose waxing more resolute. We see, without pang, castles which have crowned rocks being turned into dismantled memories, because we know that something stronger, that will defy all time, will stand ultimately on the old commanding sites. Everyone of us must work until he discovers in his work his true self, and then aid with what he finds he can do best in helping all. With everyone of us there is a mission to assist the general advance.

THE SERUM TEST FOR TYPHOID FEVER.

By GEORGE B. SHATTUCK, A.M., M.D.,
OF BOSTON.

THE cases here summed up and analyzed, in which Widal's serum test for typhoid fever was applied, were all patients in the Boston City Hospital. Seventy-three of these cases are taken from the third medical service, thirty-six from the first, and thirty-six from the second. The tests were made in the pathological laboratory under the supervision of Dr. T. Leary, of the pathological department, by the house officers of the three medical services, to whom much credit is due for zeal and intelligent industry in a task outside of their regular work. The clinical statements are necessarily subject to the unavoidable peculiarities of hospital practice, though every effort has been made to have them as accurate as possible. The date of the beginning of typhoid fever, for instance, has been assumed as the time to which the patient refers the first constitutional symptoms. The patients are not always intelligent, even when they desire to be correct. This throws unavoidable doubt upon the day of the disease when tests were made, and affects the value of conclusions drawn. On the other hand, after entrance to the hospital the patients were always under careful supervision, and both the number and variety of cases presented are considerable.

In some of the cases a larger number of tests at different periods of the disease might advantageously have been made had there been a larger force and more time at our disposal. All the tests were made with liquid blood. The test with dried blood was not tried. Only incidentally can we claim to make a contribution to the questions of the proportion of serum to typhoid culture, of the early and late periods at which the reaction may be obtained, of the existence of other blood-serums giving the same reaction. The fate of the diazo

reaction has been borne in mind, and that test has been noted in connection with a large percentage of these cases. A number of cases were rejected on account of defective records or defective tests. In the laboratory a longer maximum time limit (one hour) was allowed for the reaction than some observers would consider justifiable. Many of the reactions did occur in much less time, the character of the reaction was considered as well as the time within which it occurred, and the room culture reacts less promptly than the thermostat culture.

Of these 145 cases 125 may be set down as typhoid fever either straight or with complications; 19 were not typhoid; and 1 may, perhaps, be classed as doubtful, though reacting to the serum test.

Technique.

Dr. Leary furnishes the following statement in regard to the laboratory technique:

The cultures used at the laboratory for the serum test for typhoid fever were obtained from several sources. Three were obtained from spleens of patients who had died of typhoid fever, and a fourth from fluid aspirated from a tumor mass which corresponded in position to the gall-bladder, from a patient who was suffering from that disease. Daughter cultures from these were used, without choice, during the early tests, but shortly afterward it was thought best, in order that the conditions surrounding the tests should be as exactly alike as possible, that the cultures used should all come from the same sources. One of the spleen cultures was selected, and its progeny has furnished all of the preparations since used. Up to January 1st the tests were made with twenty-four hour bouillon cultures grown at a thermostat temperature. At that time some tests were made with cultures grown at the room temperature, and the results were so satisfactory that all tests since that time have been made with room cultures. In the room cultures the organisms, while fewer in number, are larger and more motile, and the reactions, while perhaps a trifle slower, are so absolute that little difficulty occurs in making a diagnosis. In the thermostat cultures there often is a small sediment made up of dead organisms which, if shaken up into the fluid, may interfere with a diagnosis. This sediment is much less

likely to occur in connection with room cultures. Room cultures, again, can be used for the test when much older than thermostat cultures, the growth being more gradual and the organism being hardier.

The technique as used is that commonly practised. Blood is obtained from the ear of a patient, the skin being first washed with alcohol, and a single deep puncture made with a glover's three-cornered needle. The blood is collected in a piece of glass tubing which has been sealed at one end. The open end is then plugged with cotton. The blood is brought to the laboratory and a clot allowed to form, which takes usually three to five minutes. A drop of the nearly clear serum is then placed on a glass slide and surrounded by ten drops of typhoid bouillon, the drop measure being a small loop on a platinum needle. The serum and bouillon are then thoroughly mixed and covered with a clean cover-glass, care being taken to exclude all air.

A positive diagnosis is made if before an hour has elapsed the bacilli in good part have lost their motility and have grouped themselves, not lying together in close masses or in parallel bundles, but gathered loosely as logs may be thrown together in the eddy of a river. Dead bacilli in the cultures tend to clump closely in more or less parallel masses.

An hour was arbitrarily made the limit of time for the test, since it was found that within that time satisfactory clumping would occur if it was going to occur at all. A shorter limit would have placed many tests in the doubtful column which were satisfactory at or near the end of the limit of time, and which were oftentimes repeated with success in cases of undoubted typhoid.

In the early experiments which were made here, too much, perhaps, was demanded of the test. It was expected that, in a satisfactory test, practically all of the bacilli should be motionless and grouped in masses which should nearly cover the field of a Leitz one-twelfth oil objective No. 3 eye-piece. In the later tests this has not been expected. It was thought sufficient if groups of twenty to forty organisms might be found, perhaps twice in five fields, with some organisms still showing motility.

Tests in which the number of blood-corpuscles on the slide was too great, or where much air was present in globules, were ruled out

and repeated, as were tests in which any doubt existed about the correctness of the technique or about the character of the reaction.

Analysis of the Result of the Test in 116 Cases with a Clinical Diagnosis of Typhoid.

Reaction before the 10th day:

"	6th day	1
"	7th "	4
"	8th "	6
"	9th "	5
"	between 10th and 15th day	23
"	" 15th and 20th "	16
"	" 20th and 30th "	32
"	" 30th and 40th "	13
"	" 40th and 50th "	11
"	" 50th and 60th "	5
"	" 60th and 70th "	2
"	" 70th and 80th "	2
"	" 80th and 90th "	0
"	" 90th and 100th day	0

" 100th day and over: 1 100th day; 1 110th day; 1 121st day; 1 122d day.

" 1 on the 39th day and 122d day. Relapse, phthisis.

" 1 on the 110th day, relapse; 1 on the 100th day, post-typhoidal neuritis.

" 1 on the 121st day, phlebitis.

No reaction in 1 case.

No reaction in 2 cases; one test only, on the 12th day, and one test only on the 82d day.

" " 1 case on 26th day; reaction 27th day.

" " 1 " " 15th " " 16th day.

" " 1 " " 16th and 18th days; reaction 59th day.

" " 1 " " 7th day; reaction 9th day.

" " 1 " " 18th day; reaction 45th day.

Doubtful reaction 1 case on 10th day; reaction 13th day.

" " 1 case on 20th day; reaction 26th and 28th days.

Analysis of the Results of the Serum Test in 11 Cases with a Doubtful Diagnosis.

Of these doubtful cases four gave no reaction to the serum test at any period. One of these was, without doubt in view of its whole course, a case of meningitis.

Another is a particularly instructive case. No ante-mortem diagnosis was made in the hospital. The patient entered on the 124th day of his illness, as "after typhoid." His doctor reported that the patient had had rose spots, enlarged spleen, and typical course of typhoid fever. At entrance great emaciation with bed sores; no fever. No reaction to two tests. Death. Autopsy: old malignant endocarditis.

The third case gave a negative physical examination, very vague symptoms and course; slight temperature, soon becoming normal. There was no diazo, and no reaction to the serum test on fifteenth day. The diagnosis of typhoid was entertained, but not positively made. The patient was discharged well on the twenty-ninth day.

The fourth gave a negative physical examination, and had very vague clinical symptoms and course. On account of a chill plasmodia were sought for, but not found. The diazo reaction was absent. A serum test was made on the sixth day, and was negative. Unfortunately there is no record of its having been repeated. The diagnosis of typhoid was considered, but remained in doubt. The patient was discharged well on the twenty-third day.

In five of these cases the serum test gave a positive result, and was of material service in determining a doubtful diagnosis.

In the first of these cases the physical examination was negative; symptoms were absent, but there was some temperature. It was said that there had been cases of typhoid fever in the neighborhood of the patient's home. The serum test gave a good reaction on the twenty-second, twenty-third, and twenty-fourth days.

The second case was that of a professional man, a private patient, fifty-two years of age; a rather steady drinker. Six weeks before entrance, while in another city on important business and subject to some strain from work and anxiety, he suddenly became mentally confused for a short time, though not entirely losing consciousness. From this he recovered entirely. Two weeks later, at home, he had another similar attack, with incomplete recovery mentally. He was slow in expression and miscalled words. A week before entrance the left leg was noticed to be swollen and painful on pressure. There were blood, albumin, and casts in the urine. The attending physician, an excellent practitioner of large experience with typhoid fever, had diagnosticated serious renal disease and given a grave prognosis.

He entered the hospital thirty days from the beginning of the illness, with weakness, loss of appetite, and mental confusion. The edge of the spleen was felt, otherwise the physical examination was negative. The temperature might have been that of the end of typhoid. There was no diazo. The clinical diagnosis was reserved. The serum test gave a prompt reaction, and the patient made a good recovery as from typhoid fever.

The third case was considered as probably meningitis, and the symptoms pointed strongly in that direction. Two separate serum tests, at a period of the disease which could not be specified, gave positive reactions. The patient recovered. This was probably a typhoid with meningitis.

The fourth case presented a normal temperature two days after entrance. History suggested, as a possible diagnosis, the end of an ambulatory typhoid of six weeks' duration. The serum test gave a positive reaction on the forty-second day.

The fifth case was considered as perhaps one of uræmia. History and symptoms vague. There were œdema, delirium, slow pulse, enlarged spleen, strabismus, nystagmus, retraction of the neck, twitchings. There were prompt reactions to the serum test on the sixteenth and nineteenth days. Death. No autopsy.

In two doubtful cases the serum test gave both a positive and a negative reaction on different days. In one of these cases gastritis was suggested as a provisional diagnosis. The physical examination was negative, the symptoms and course very vague. On the seventh day there was a positive reaction to the serum test, and on the eleventh day no reaction. Herpes appeared on both lips on the eighth day. No diazo. This patient was discharged well on the fifteenth day. In the other case the history was rather typhoidal, the symptoms and course were very vague. There was no reaction to the serum test on the fifteenth and eighteenth days, and a good reaction on the twenty-second day.

Analysis of the Result of the Serum Test in 18 Cases with a Clinical Diagnosis Other Than Typhoid Fever.

There was no reaction in fifteen of the above cases, of which two were pneumonia, two pleurisy, four meningitis, three "febricula,"

one was phthisis, one acute miliary tuberculosis, one appendicitis, one influenza.

There was a reaction in three of the above cases, of which one was pneumonia, one was thought to be acute miliary tuberculosis, one was exophthalmic goitre. In all three of these cases the typhoid reaction was justified, and the test made the diagnosis. In the case of pneumonia the test was made on the fifteenth day of the illness; the patient died on the twenty-second day; there was no autopsy, but there is little doubt that there were both pneumonia and typhoid fever.

In the case of exophthalmic goitre the symptoms were masked and confusing, and typhoid was not at first suspected. Three distinct tests were made not earlier than the twentieth day; all gave a positive reaction. The patient eventually died of pneumonia on the forty-third day after entrance to the hospital, and the autopsy showed small but characteristic typhoid ulcers nearly healed.

In the case diagnosticated as acute miliary tuberculosis the symptoms and course were perplexing, but on the whole justified such a diagnosis, and an unfavorable prognosis was given. The patient later developed diphtheria, was transferred to the diphtheria department, and while there as a convalescent, on the sixty-ninth day, the serum test, which was not being practised when he first entered the hospital, was made and gave a prompt and positive reaction. This case recovered.

The Test with Negro Blood.

The query having arisen[1] whether serum from the blood of the negro was more prone than that from the white to produce the reaction even in the absence of typhoid fever, tests were made by Dr. Leary, at my request, with serum from thirteen colored patients, of various admixtures, but the majority negroes, in the hospital, with clinical diagnoses other than typhoid. In eight of these there was no reaction. In three there were reactions more or less satisfactory with thermostat cultures, but none with room cultures. In two there were good reactions both with "stat" cultures and with room cultures. Of these two, one was a black negress, the other a mulatto

[1] J. W. Brannan, M.D., N. Y. Medical Journal, March 27, 1897.

born in Africa. They were both surgical patients. In each case the *status præsens* and the history were carefully gone over. They certainly have not had typhoid fever since entering the hospital. Typhoid cannot be excluded from the histories of the previous six months, but the symptoms and conditions reported can be better explained by other causes, and without the result of the serum test typhoid would certainly not have been considered. These cases have not been included in the 145 previously analyzed.

The Diazo Reaction.

This reaction was sought for in the urine and the result recorded in eighty-nine cases out of the 125 cases of typhoid fever; it was found in forty-two cases, and not found in forty-seven cases. In one case the diazo reaction, curiously though properly enough, was present on the fifteenth day, when the serum reaction was absent, and absent on the fifty-ninth day, when the serum reaction was present.

Conclusions.

1. The serum reaction may be obtained toward the end of the first week of typhoid fever, but is both more pronounced and more usual later in the course of the disease.

2. It may be present without a relapse at the end of the fourth month.

3. It may be absent one day and present the next.

4. Of 125 cases of typhoid fever the reaction was absent in only one case. In two cases it failed, but there was in each only one test, in one case on the twelfth and in the other on the eighty-second day.

5. In nineteen cases of other diseases clearly uncomplicated by typhoid there was no reaction.

6. In one case, where the diagnosis must remain doubtful, although typhoid cannot be positively excluded, there was a reaction.

7. In a number of difficult and perplexing cases the serum-test was of distinct service in establishing or correcting the diagnosis.

8. This test will probably prove itself a useful aid to clinical diagnosis, and especially in hospital practice.

DISCUSSION.

DR. A. C. ABBOTT: The conditions surrounding the application of this test to municipal work are by no means so favorable to precision as are those under which Dr. Shattuck's observations were made. Nevertheless the results that have been obtained by us in the laboratory of the Board of Health of Philadelphia are of such a nature as to speak very strongly for the usefulness of this test as an aid to the diagnosis of typhoid fever. The method that we have used is that recommended by Johnston, of Montreal.

Between February 16th and May 1st of this year samples of dried blood from 164 cases have been sent to us for examination. Of these we have received satisfactory clinical histories in 115 instances. Of the 115 cases 68 were typhoid fever *clinically*. The laboratory diagnosis by the blood-test corresponded with the clinical diagnosis in 66 of these 68 cases, making an error of 2.9 per cent. The test was negative with the bloods from the remaining 47 of the 115 cases. With regard to the stage of the disease in which the diagnosis can be made by this test our statistics are as follows: In 23 cases we could make the diagnosis within the first week. In 4 of these cases the test was positive on the third day; in 5 on the fifth day; in 6 on the sixth day; and in 8 on the seventh day. The latest period of the disease at which we have been requested to make the test has been the forty-second day, in 3 cases. In 2 cases the primary test was negative, while the secondary test at a later date was positive; the first of these was negative on the fifth and positive on the eleventh day, while the second was negative on the sixteenth and positive on the twenty-fourth day. In 7 cases the primary examinations, falling between the fifth and the tenth days, were doubtful, while secondary examinations, falling between the ninth and the thirty-seventh days, gave positive reactions. In short, in about 33 per cent. of our cases a positive diagnosis could be made within the first seven days of the disease. It is my belief that this percentage is lower than that which could be obtained in hospital work where the cases are more constantly under observation, and certainly under more favorable circumstances for the study of this phenomenon.

Of the two cases in which the laboratory test failed to confirm the clinical diagnosis of typhoid fever, one was an insane case from which a very imperfect clinical history was obtained. In this case the blood-test was negative on both the sixth and the fourteenth days. The second case was at first thought to be influenza; later, to be typho-pneumonia. It resulted fatally with hemorrhage from the bowels. There had been no enlargement of the spleen, no rose spots, and no delirium. The test was negative on the twelfth day.

We have examined the blood from four cases of diabetes, in all of which the test gave *negative* results.

DR. J. H. MUSSER: In the later stages of typhoid fever the occurrence of the reaction may lead to confusion. A patient was admitted to my wards in the fifth week of illness, and said to have had typhoid fever. Although there was high temperature there were no symptoms of typhoid fever, and it seemed he had some terminal infection. The reaction was pronounced. Three days after admission the symptoms of meningitis were pronounced. Death resulted on the seventh day after entrance. The autopsy proved that the meningitis was a terminal infection of typhoid fever.

DR. OSLER: I have asked Dr. Block, the Assistant in Bacteriology in the Medical Department, to give me a brief memorandum of our experience at the Johns Hopkins Hospital.

The Widal reaction has been tried in forty-four cases of typhoid fever, in all of which except three the reaction was present. Two of these cases were mild and atypical, and may possibly not have been typhoid fever.

In the remaining case the test was made upon the third day of a relapse which followed an afebrile period of twenty-five days, and again on the eleventh day, when the temperature was about normal. The increase in the reaction shown by the latter specimen may be considered as sufficient for diagnosis, although it was not very marked.

Ninety-six specimens of typhoid blood have been examined, and only twelve of these failed to give sufficiently marked reaction. They were, however, made either very early or very late in the course of the disease, except in the three cases just mentioned. The earliest date at which we have obtained a marked reaction was the sixth day of disease. It is found to gradually increase and gradually diminish as the disease progresses and declines.

In a case of typhoid fever occurring in a man who had had an attack the year before, the reaction was very marked. Three months later he returned with probable cholecystitis, and the question arose as to his having a third attack of typhoid fever, which was disproved by the total reaction and the subsequent course of the disease.

We have used the test-tube method macroscopically, and the serum and dry methods microscopically, and find that for practical purposes the latter is the more convenient. The test seems particularly satisfactory in excluding the various forms of tuberculosis (meningeal, peritoneal, pulmonary).

In the following cases the test gave interesting and valuable results:

S. J. (surgical patient) was admitted to hospital for streptococcus infection of the arm. Six weeks after admission the patient had a slight chill, and the temperature rose to 103.4°. There was slight headache; the tongue was coated, and there were anorexia, diarrhœa, and enlarged spleen. The temperature for over three weeks ranged between 102° and 104°. The examination of the blood gave very marked clumping and total loss of motility. This case is interesting from the fact that the general condition of the patient was not at all suggestive of typhoid fever, and, despite the symptoms enumerated above, the diagnosis of typhoid fever could not have been satis-

factorily made without the agglutination test. Cultures from the stools and blood did not show the typhoid bacillus, while the streptococcus was repeatedly obtained from the arm lesion; but it disappeared entirely long before the temperature was normal or the agglutination showed signs of lessening.

D. B., female, was admitted with delirium, and no history could be obtained. The blood did not give the agglutination test, and there was a leucocytosis of 23,000. On the next day the history was obtained from the doctor. She had complained for twelve days of severe headache, slight stiffness of the neck, and nervousness. The temperature ranged between 100° and 102.5° F. The patient had epistaxis twice; pain in the abdomen, and twenty or thirty spots on the abdomen which were stated to be identical in appearance with rose spots. She had been delirious since the day before admission. The physical examination revealed very little. The continued absence of the Widal reaction, the subsequent development of inequality of the pupils, *tâche cerebrale*, and the rigidity of the arms and neck, with the presence of sugar in the urine, led to the diagnosis of tubercular meningitis, which was confirmed by the post-mortem examination.

DR. HERMANN M. BIGGS: In using Widal's test in New York we have found that more satisfactory results were obtained by the use of serum taken from blisters than from the use of either dried or fluid blood. The serum is collected from a small blister in a capillary tube. A blister one-half inch in diameter is produced by the use of a cantharides plaster.

It has seemed to us that special emphasis should be placed upon the quantitative character of the test. It is a quantitative and not a qualitative test. A diagnosis of typhoid is not made unless the reaction is present, when the proportion of blood to fluid is one to ten, or more. Where a less dilution than this of the blood is present the reaction may appear not infrequently in blood derived from other than typhoid fever. In my own service at Bellevue Hospital I have, in several instances, sent specimens of blood to various bacteriologists in the city and received a positive diagnosis of typhoid fever in cases which were certainly not typhoid fever—diagnosis having been based upon the presence of a reaction in the dilution of the blood of less than one to ten.

DR. I. E. ATKINSON: There is one question I would like to ask. How long does the reaction persist in cases of typhoid fever? Persons who have had typhoid fever remain susceptible to the test for some time, and if the blood be examined during a subsequent illness, even though it be not typhoid, the characteristic reaction will be obtained. We do not get the Widal reaction in persons who have had typhoid fever long since, and I would like to know how long this susceptibility remains.

DR. JAMES TYSON: Two observations in the use of Widal's test have occurred to me which may be of interest. The first has some bearing on the possible service it may render us in the recognition of aborted cases of typhoid

fever, the occasional occurrence of which is, I believe, admitted. Two young girls, aged about twenty and twenty-four years, skated from three to six o'clock for three days in succession on the Schuylkill River. These days were December 27th, 28th, and 29th. Both had been very busy socially for a week or more previous, and were very much tired out. On December 27th, being very thirsty, they drank of the river water through a hole in the ice. On Thursday evening, December 31st, they were both taken with fever, which continued, but I did not see them until Sunday evening, January 3d, just one week after the ingestion of the water. I found them both with decided fever and headache, and that the elder girl, B, had bled at the nose twice since the initial fever had set in. The younger, C, had two spots on the abdomen, which acted precisely like the spots of typhoid fever. At the end of one week, however, the younger girl, C, was free from fever. The elder, B, continued to have fever for three weeks longer, and then it gradually abated. On Monday, January 25th, a specimen of blood of this girl B was given to Dr. Kneass, of the Pepper Laboratory, who recognized the Widal reaction. At no time did either of the girls have diarrhœa. B never had any spots, while C, whose case aborted, had only the two referred to. In addition to the primary nose-bleed, B had nose-bleed twice in the third week. On about March 15th specimens of the dried blood of each of the girls were sent to Dr. Kneass, who replied as follows: "An examination of the first specimen that you sent me, 'B,' gave a positive but somewhat slow reaction. Case 'C,' sent at the same time, gave a very incomplete reaction; some agglutination and loss of motility being present. It is probable that this case would have shown a positive result if it had been examined at the height of the disease. These facts correspond with other results, that in light cases the Widal reaction may disappear rapidly during the defervescence."

The second observation involves an error of diagnosis which probably would not have occurred if the evidence of the test had been accepted: F. H., an apothecary, aged about twenty-five years, was admitted to the hospital of the University of Pennsylvania on March 2d, said to be in the seventeenth day of a typhoid fever, having been, up to this time, under the care of a well-educated physician outside the hospital. There had been considerable temperature, 103° and 104° F. being attained, but it was not systematically recorded. There was obstinate cough with crepitant râles at the bases of the lungs, but no dulness to percussion, or bronchial breathing. Even epistaxis was said to have occurred, while one or two spots were reported on the ninth day. The diazo-reaction was also present. There was, however, no diarrhœa. On admission his temperature was only 100° F. at 10 P.M., but rose to 102.8° at midnight. The belly was slightly tumid, and gurgling could be elicited by pressure in the right iliac fossa, but there was no tenderness. There were no spots, but the spleen was appreciably enlarged to percussion. There was cough, with expectoration of whitish and greenish masses, sometimes tinged with pink. *The Widal test was negative, but we held to the diagnosis.* He was not tubbed immediately after admission, but it was thought that he was probably well advanced into the fastigium. Indeed, his temper-

ature, after the primary rise, hung about 102° F., confirming, from this standpoint, our conclusion. On the afternoon of the third day, however, it reached 103¼°, when tubbing was commenced, and subsequently discontinued because of his strenuous objection. He, moreover, bore it badly, being quickly cyanosed; indeed, was cyanosed more or less continuously. It was subsequently renewed, but again discontinued. Our erroneous conception of the stage in which we had supposed he was was also sustained by the very prompt and marked decline of temperature which followed the baths, a drop of three degrees almost always occurring. He declined rapidly, and was ultimately removed from the hospital just before death, which occurred on the 13th of the month. The autopsy revealed a miliary tuberculosis of the lungs, but none of the lesions of typhoid fever except the enlarged spleen.

DR. FRANK BILLINGS: I have had considerable experience with Widal's test in Mercy Hospital in Chicago, where it is the approved practice in the diagnosis of typhoid fever. I was glad to hear this paper of Dr. Shattuck's; I was glad to hear what Dr. Abbott had to say in regard to it, and I would like to ask Dr. Biggs about the proportion of serum to culture used in his tests. It may be that the failures in his cases were due to faulty technique, or to not fully carrying out the directions given by Widal and Johnston. One of the printed instructions given by Johnston states that old cultures should be used for the test. Later, however, he explains that the old culture should be used as a basis, and a new culture made from that. Old cultures are rather easily killed by the blood serum of very many cases, and especially is this true in many cases of septicæmia and other surgical diseases. The test is more constantly positive in typhoid fever, and more constantly negative in other diseases. A clear understanding of the technique and the age of the serum are essential factors in the use of this test. In reply to Dr. Atkinson's question as to the duration of the susceptibility of typhoid fever to this test, I may say that one of the internes at the Mercy Hospital had an attack of typhoid fever three years ago, and that he still reacts to the Widal test. Widal states that seven years is the longest term in which he has found the reaction to persist.

DR. JAMES T. WHITTAKER: An individual case may throw a side light upon this question. A physician brought his daughter to see me. She was listless, suffered from headache, and had a temperature of 100°. She had been ill three months. He had found albumin in her urine, and thought she was suffering from Bright's disease. There was slight albumin in the urine, but the specific gravity was normal. The diazo reaction was present. After examining her I came to the conclusion that it was a case of latent tuberculosis, and gave her a stout injection of tuberculin, but got no reaction. It then occurred to me to test the case with Widal's test, and it reacted promptly. I tried the Widal test at intervals four times, and then felt justified in the diagnosis of ambulatory typhoid, or protracted convalescence from typhoid fever.

DR. F. C. SHATTUCK: In the latter part of November, 1896, I saw a lady in consultation. October 1st she had broken her leg by a bicycle fall. Seven days later, while in bed in splints, fever came on. The urine was found to be albuminous, and the case was regarded by her attendants as one of acute Bright's disease. The fever was continuous for three or four weeks, and nervous symptoms were regarded as uræmic. There was, and had been, no typhoid fever in the place, a fashionable summer resort. The temperature-chart and the whole group of symptoms—both fever and albumin had disappeared when I saw her—made me strongly suspect that she had had typhoid fever with a somewhat unusual degree of renal implication. This suspicion was converted nearly into absolute certainty, in my mind, by finding that the dried blood gave a typical Widal reaction. The test was here of much value, as it enabled me to give positive assurance that no anxiety need be felt for the future as far as the kidneys were concerned, an assurance which brought the greatest comfort to the family.

DR. EDWARD G. JANEWAY: I wish to say a few words about the dangers in the use of this test. Sufficient evidences of its usefulness have been cited, and now a word of warning is called for. The danger lies in the tendency to rely too implicitly upon the negative test where all the physical symptoms of typhoid are present. I saw one case which illustrated the danger of this tendency. I was called to see the patient in consultation on the twenty-eighth day, after two negative reactions, according to Widal, had been obtained. Yet I could call the case, as the other physicians did, nothing but one of typhoid, despite the absence of Widal's test. I saw the patient again on the thirty-fifth day in a state of collapse with perforation of the bowel, and on this day there was a first reaction to the test. The danger lies in the tendency of some persons to regard this as what some persons would call a pathognomonic test. The general medical public read of these things and come to look upon such tests as final. They hear nothing of the negative reactions that have resulted, but they read all that is said by prominent men who have tried it with success.

GALL-BLADDER INFECTION IN TYPHOID FEVER,

With the Report of a Case in which Tapping the Gall-bladder Resulted in Cure.

By A. LAWRENCE MASON, M.D.,
of Boston.

Inflammation of the gall-bladder, sometimes resulting in ulcerative perforation or in rupture from distention, with consecutive peritonitis, has long been noted as an occasional complication in fatal cases of typhoid fever. The clinical evidences of this condition have usually been masked by the general abdominal symptoms of the disease, so that the localization of pain or tumor in the region of the gall-bladder, and the recognition of this appendage as the immediate source of danger, have not been practicable. Therefore most of the recorded cases, some forty in number, have been post-mortem discoveries; or, if the state in question has oftener been surmised at the bedside, it has seldom been the subject of accurate observation or of surgical interference. There are a few instances, however, in which this localized inflammation presents such striking symptoms that its seat and nature can be determined, and thus impending danger may be averted. Such an instance affords the basis for this paper, in which I will relate the history of a case of typhoidal cholecystitis, and then refer to the literature bearing upon this subject and the deductions to be drawn therefrom.

Case. A woman, aged thirty years, entered the Boston City Hospital in the third week of typhoid fever, with dry, brown tongue, palpable spleen, rose spots, and distended abdomen. Anorexia, vomiting, and constipation had been prominent symptoms. Widal's serum test was positive, but not immediate; clumping of bacilli and loss of motility in fifteen minutes. 9600 leucocytes. Typhoid deafness. Toward the end of the third week she complained of in-

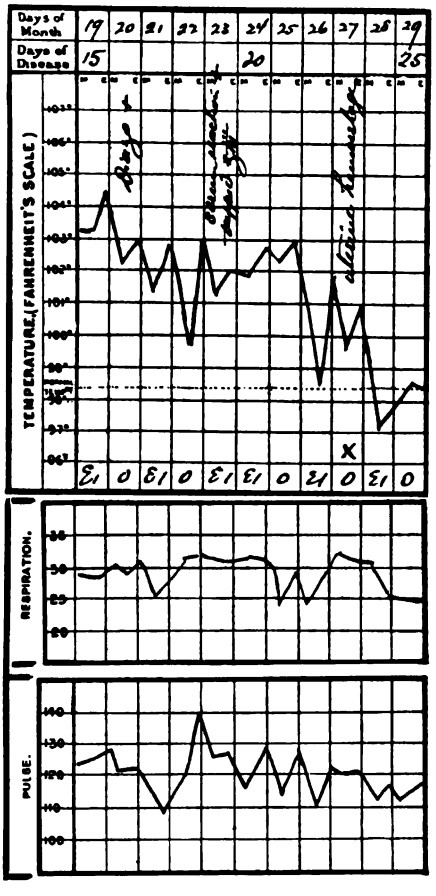
creasing abdominal pain, that became localized in the right hypochondrium, where a tumor four inches in diameter developed, extending from the costal border toward the umbilicus. This tumor caused a visible swelling, was very tender, absolutely dull on percussion, and descended on full inspiration. At the time of admission, a week earlier, the liver dulness had been normal, and there was no special pain in this region. Now the patient's condition showed partial collapse, and as suppurative distention of the gall-bladder was thought to be present, my surgical colleague, Dr. George W. Gay, saw her in reference to an early laparotomy, because rupture of the gall-bladder

FIG. 1.

seemed imminent. Her state was regarded as unfavorable to the success of a capital operation; therefore I at once tapped the gall-bladder at a point one inch below the costal margin and four and a half inches from the umbilicus. Three and a half ounces of sero-purulent fluid were withdrawn, pale in color, looking more like urine than bile. The aspirating-needle moved up and down with the action of the diaphragm. No gallstones could be felt with the point of the needle. After its withdrawal a pad and swathe were applied to prevent the escape of septic fluid into the peritoneal cavity. The relief to pain was immediate. The next day all urgent symptoms had disappeared and they did not return. The pulse fell from 140 to 120, and defervescence followed in five days. The gall-bladder gradually retracted, convalescence ensued, and when the patient returned for observation a month later nothing

abnormal was found in this region. A photograph (Fig. 1) and chart (Fig. 2) are herewith presented, together with a specimen of the fluid withdrawn.

FIG. 2.



The following report was made by Dr. R. M. Pearce, assistant to Dr. Councilman in the Pathological Laboratory of the City Hospital:

"The fluid is of a pale yellowish color, watery consistency, and fecal odor, with considerable fine yellowish sediment, in which fine reddish-yellow granules could be seen. Sp. gr. 1016; albumin 1 per cent.

"Fresh examination, microscopically, shows much bile-pigment, numerous cholesterin crystals, pus cells and epithelial cells, most of the latter being granular and some fatty.

"Sediment stained with Loeffler's methylene-blue shows pus cells, epithelial cells, and numerous short, thick bacilli with rounded ends, occurring singly and in pairs, and usually in the pus cells, arranged in clumps around the nucleus.

"Cultures show round, flat colonies with elevated centres of pale white color, almost transparent; microscopically short, thick bacilli with rounded ends and very motile. No other bacilli.

"Cultures from dilutions, planted on potato, produced invisible growth; in litmus milk no reddening or coagulation; in sugar gelatin no gas-production. Flagella stained.

"With serum from a known typhoid case characteristic clumps with loss of motility were produced. The same reaction was produced with the patient's own serum.

"Diagnosis: typhoid bacillus.

"*Dec. 7th*, 3 P.M. A guinea-pig was inoculated subcutaneously with 1 c.c. and 1 c.c. intraperitoneally of forty-eight hour bouillon culture. A large subcutaneous abdominal abscess developed, which burst and discharged.

"*20th*, 1 P.M. Pig killed. Autopsy showed general œdema of abdominal tissues; marked enlargement of inguinal and axillary glands; large slough 2 cm. in diameter at seat of inoculation; fluid in abdominal and pleural cavities; marked enlargement of mesenteric and retroperitoneal glands; spleen enlarged, reddened, follicles distinct; Peyer's patches enlarged; intestinal tract otherwise normal. No changes apparent in other organs."

Dr. S. W. Ellsworth, house physician, used pure cultures of the bacilli found in this fluid in further clinical tests for Widal's reaction, as follows:

With the serum from eight cases of typhoid fever the characteristic clumping and loss of motility were quickly obtained.

With serum from one case each of malaria, pneumonia, phthisis, and rheumatic fever the results were negative, as they also were in further testings of the serum from these cases with a pure culture of typhoid bacilli from a spleen.

The records of the Boston City Hospital, so far as I am aware, contain but three other cases of this complication in typhoid fever, and these occurred in the same family, as reported by Dr. C. Ellery Stedman in *Third Series of City Hospital Reports*, 1882.[1]

They are, briefly, as follows:

CASE I. A girl, aged thirteen years, died on the twenty-fourth day with symptoms of peritonitis. At the autopsy the usual lesions of typhoid fever were found, and in addition adhesive inflammation in the region of the gall-bladder, which was glued to the colon at the junction of the ascending and transverse portions. The fundus of the gall-bladder was ulcerated and ruptured, and there was a pint and a half of yellowish serum in the abdominal cavity. No gallstone.

CASE II. A girl, aged six years, sister of the above, died of typhoid fever on the twenty-eighth day, and the post-mortem examination showed extensive peritonitis, with a pint of sero-purulent fluid in the abdominal cavity. There were three perforations of the gall-bladder and extensive ulceration of its inner surface.

CASE III. Male, aged sixteen years, brother of the above, developed a tender, rounded tumor in the region of his gall-bladder in the second week of typhoid. This gradually subsided and the patient made a good recovery.

LITERATURE. In examining the history of this subject during the past sixty years we find some forty cases recorded in which destructive inflammation of the gall-bladder during typhoid fever has attracted attention as a matter of special interest, usually after death. Few of the earlier, and almost none of the later, works on medicine give it more than a passing mention, and the unusual localization of this lesion, so "bizarre," as it was termed by a French writer, has until recently found no satisfactory pathological explanation.

Louis, in his work on *Typhoid Fever*,[2] states that "changes in the bile and gall-bladder are much more frequent in the course of the typhoid affection than in that of other acute diseases." He cites three fatal cases in which cholecystitis, unrecognized during life, had supervened. In two the gall-bladder was filled with a "transparent, aqueous, diaphanous, or urinous liquid," and in one the cystic duct was obliterated.

Similar cases are mentioned by Andral, Grissolle, and by other writers in the French journals since 1835, to which reference is made at the end of this article.

In the German writings before 1890 are several communications based upon the discovery of post-mortem typhoidal lesions of the gall-bladder, but I will mention only the observations of Rokitansky and Frerichs, and Hölscher's autopsy records.

Rokitansky[3] speaks of fibrinous exudations of a "diphtheritic" character as occurring within the gall-bladder and ducts in typhoid fever, cholera, and pyæmia, their existence being indicated by no symptoms during life, and only determined by post-mortem examinations. This is not an adequate description of the process under discussion.

Frerichs,[4] on the other hand, found the gall-bladder filled with a turbid, ash-colored, albuminous fluid, of neutral or feebly alkaline

reaction, in three cases of typhoid fever and one of typhus. In two cases bile-pigment and biliary acids were entirely absent; in the other two small quantities of these substances and some leucin were found. The lining membrane of the gall-bladder and ducts was softened and pale. There were no gallstones, and no jaundice or other hepatic affection was present.

Frerichs also gives the following description of a case that recovered:

Case. A female, aged twenty-six years, on the thirteenth day of a typhoid fever had attacks of vomiting, and two days later a very painful, pear-shaped tumor was found in the right hypochondrium in immediate connection with the liver above. It gave a muffled, tympanitic percussion-tone. There were no signs of biliary obstruction. Leeches and cataplasms were applied. The vomiting ceased altogether; nausea continued for many days. Pain and tension diminished, and the boundaries of the tumor contracted until, in the fourth week, convalescence ensued, although the gall-bladder could be felt for a long time.

There is a noticeable similarity between this history and that of my case, except that the withdrawal of the fluid enabled us to determine both its source and its cause by methods that were not formerly available.

In Hölscher's[5] 2000 typhoid autopsies marked hepatic degeneration was found in more than ten per cent. of the cases. In twenty-two only was jaundice present, and in but five was purulent inflammation of the gall-bladder discovered. In a single case there were perforation and circumscribed peritonitis.

Courvoisier,[6] in his elaborate work on the *Pathology and Surgery of the Biliary Passages*, records ten fatal cases of typhoid cholecystitis, two with gallstones and phlegmonous infiltration of the gall-bladder walls, and seven with sero-purulent exudate, occasional ulcers and necrotic areas. In four cases of perforation no gallstones were present.

Among English authorities Budd[7] relates a case which came under his care in 1849:

Case. A female, aged eighteen years, entered King's College Hospital in the second week of typhoid fever. During the third week she lay delirious, on her back, with legs drawn up, and gave signs of pain when the region of the liver was pressed upon. "On the nineteenth day," says Dr. Budd, "when

I made pressure on the belly to the right of the epigastrium she uttered a loud shriek. I now discovered a fulness in that part of the belly, and inferred that there was inflammation of the gall-bladder or that an abscess existed in the liver." Chills and vomiting followed, but the patient lived two weeks longer. There was no jaundice. Autopsy showed a distended gall-bladder an inch and a half below the liver-margin with recent peritoneal adhesions to the surrounding parts. It contained considerable puriform fluid and fourteen gallstones, one of which completely blocked the cystic duct. They consisted of cholesterin with nuclei of inspissated bile. The liver itself presented no unhealthy appearance. Extensive ulceration of Peyer's patches.

Budd remarks that "suppurative inflammation of the gall-bladder seems especially liable to occur when by any cause the cystic duct is permanently closed." He regards the purulent and ulcerative inflammations of the gall-bladder in typhoid as similar to the appearances observed in the violent remittent fever that prevailed with great fatality among the British troops on the Island of Walcheren in 1809, in the fever of Sierra Leone, and in yellow fever.[8]

Murchison, Harley, and Hale White make special reference to the cholangitis and cholecystitis that may attend typhoid fever.

Murchison[9] states that in this disease "fatal peritonitis may result from ulcerations of the gall-bladder proceeding to perforation." He cites the case of a youth who on the fifteenth day was seized with symptoms of peritonitis and died within twenty-six hours. The cause of death was perforating ulcer of the gall-bladder which had allowed bile to flow into the peritoneum.

This author further says: "The lining membrane of the gall-bladder is very liable to become inflamed in enteric fever without producing any marked symptoms during life. This inflammation is sometimes catarrhal, with pus-formation; at other times, according to Rokitansky, it is diphtheritic; thirdly, it may take the form of ulceration, as in cases recorded by Andral, Jenner, and Trousseau, and the process may end in perforation and fatal peritonitis. In a large proportion of cases, when the disease has lasted three or four weeks, the bile is thin, watery, almost colorless, of low specific gravity, 1010 to 1016 instead of 1025 to 1030."

Murchison mentions several other cases by different authors as well as in his own practice.

Harley,[10] after commenting upon the usual hepatic degeneration in typhoid, says that he constantly found the bile thin, watery, and of

low specific gravity, giving slowly and faintly the characteristic reactions when tested with the mineral acids or by Pettenkoffer's test. It was sometimes excessively acid, and in one case, examined twelve hours after death, had a strong smell of sulphuretted hydrogen. Harley's view of these biliary changes is that the hepatic secretion becomes vitiated either by prolonged vascular congestion or through "the effect of some morbific agent carried by the portal vein from the intestinal surface into the liver," which may, at an early period in the disease, cause torpidity of that organ and more or less complete cessation of its function.

Although our own authors have not made such extensive reference to the biliary complications of typhoid fever as the writers to whom I have referred, they mention the danger to life that may arise from suppuration within the gall-bladder; and beside the cases of Dr. Stedman, previously quoted, I have found a few others.

Dr. Daniel Ayres,[11] in 1846, described "A Case of Perforating Ulcer of the Gall-bladder Complicating Continued Fever:"

Case. A young hospital interne, during convalescence from typhoid fever, was taken with acute pain in the right hypochondrium, and died of peritonitis. At the autopsy a perforating ulcer at the fundus of the gall-bladder was found, and the abdominal cavity contained ten ounces of biliary fluid, serous in character. The ducts were patent and there were no gallstones.

Ayres mentions the cases of Budd and Louis, which were then recent, and, after alluding to their analogy in this respect with yellow fever and other diseases of tropical climates, in which inflammation and ulceration of the gall-bladder may occur as a sequence to biliary derangements, he concludes that "perforation generally supervenes upon a previously diseased state of the gall-bladder, and very rarely appears in the course of acute disease without such a cause."

An interesting case is reported by Dr. William Pepper in 1857,[12] and is quoted by Frerichs as bearing upon this subject:

Case. A man, twenty-six years old, had a prolonged bilious fever, and came under the care of Dr. Pepper six months later with severe pain and a tumor in the right hypochondrium which gradually extended as far as the crest of the ilium. It was tapped and a few ounces of muco-purulent fluid were withdrawn. After death the gall-bladder was found enormously distended by two quarts of semi-purulent fluid. The walls were ulcerated, and the cystic duct was completely closed by exudate. No gallstones were present. There were two small abscesses in the right lobe of the liver.

The most comprehensive study that had then appeared (in 1876) is contained in the Paris Thesis on "Cholecystitis in Typhoid Fever," by Hagenmüller.[13] Eighteen cases from French and German reports are collected. In four cases there was slow recovery; in the others death from peritonitis, the affection of the gall-bladder having been unrecognized during life. Hagenmüller's conclusions were that typhoidal cholecystitis, apparently so rare, will be more frequently observed when attention is awakened to the subject; that it results from the propagation of the intestinal inflammation to the gall-bladder owing to low systemic conditions; that the diagnosis must be based upon the localization of pain in the right hypochondrium or in some cases upon intumescence of the gall-bladder; and that fatal peritonitis may result from perforation or from simple extension of the inflammation to the peritoneum by contiguity. In but two cases were gallstones found, and rarely did the inflammation involve the liver-substance.

During the past decade only has it been possible to apply the methods of bacteriological research to these obscure lesions and to trace the gall-bladder infection directly to the typhoid bacillus.

In 1890 Gilbert and Girode[14] reported the first case of suppurative cholecystitis caused by the invasion of typhoid bacilli as demonstrated microscopically and by cultures. In 1893 the same authors presented a further communication relating to the same subject.[15]

Case A woman, aged forty-five years, during a moderately severe typhoid fever had symptoms referable to the gall-bladder—pains and a swelling in that region. With convalescence the swelling diminished, but after a considerable interval the symptoms returned, and on readmission to the hospital, five months after the termination of the typhoid attack, cholecystotomy was performed. The gall-bladder contained pus which gave a pure culture of typhoid bacilli, and there was also a small calculus.

E. Dupré, in a comprehensive thesis on "The Biliary Infections,"[16] gives two cases (Observations VII. and IX.) in which he had made pure cultures of the typhoid bacillus from the gall-bladder. The first was that of a man, forty-six years old, who died on the sixteenth day of his fever. Although the gall-bladder presented no apparent pathological changes, pure cultures of Eberth's bacillus were obtained. The second observation relates to a woman, forty-five years old, who died from an operation for gallstones, performed six months after

recovery from typhoid fever. The discovery of typhoid bacilli in these gall-bladders led the author to think that this infection was more common than was supposed.

In 1892 Guarnieri[17] found infection of the biliary passages, liver, and spleen by the typhoid bacillus in a case that presented no intestinal lesions.

Chiari's[18] report of a case of destructive cholecystitis, in which the pathogenic organisms of typhoid fever were found, was one of the first on this subject.

Case. A boy, twelve years old, after six weeks' illness with typhoid fever, died apparently of a terminal pneumonia. At the autopsy the classic intestinal lesions of typhoid fever in a convalescent state were found, also bronchopneumonia. The gall-bladder was full of pus and had several necrotic patches on the walls. Externally was a fibrinous exudate with adjacent peritonitis. The biliary ducts and duodenum were normal. The cause of death was cholecystitis which had provoked peritonitis. Typhoid bacilli in pure cultures were found in the pus and in the gall-bladder walls.

The author regarded his case as second to the one reported by Gilbert and Girode.

Chiari[19] made a further report to the International Medical Congress in Rome, giving the results of his examinations of twenty-two patients who died of typhoid fever. In three only were the typhoid bacilli absent from the gall-bladder. In fifteen they were the only kind, and the number was often very great. Inflammation of the gall-bladder had occurred in thirteen cases, in twelve involving only the mucous lining, in one the whole wall, and causing a secondary peritonitis by extension. Chiari concludes that the occurrence of typhoid bacilli in the gall-bladder is the rule in typhoid fever, and that they increase and may remain there a long time; finally, that they may cause gallstones and relapse.

There are several questions of interest that suggest themselves in connection with these various reports, clinical and pathological.

1. How do the germs reach the gall-bladder?

2. Have they a special predilection for previously damaged gall-bladders, or those containing gallstones?

3. Is it probable that typhoid fever may cause gallstones?

4. What are the means available for diagnosis and treatment?

CHANNEL OF INFECTION.—The sterility of normal bile is not

questioned so long as the ducts are pervious and the flow is free, but when there is disease of the biliary passages by which the bile-current is checked micro-organisms from the duodenum find easy access to the gall-bladder. Charcot and Gombault, after tying the common duct in animals, found that the bile above the ligature was infected by bacteria within a short time. Numerous other observations have confirmed this, and Létienne[20] examined the bile immediately after death in forty-two patients who died of various diseases, finding micro-organisms in twenty-four, or more than half. The bacterium coli commune was often observed, but there seems to be no reason why this germ should not always invade the gall-bladder after death. Naunyn[21] found it in the fluid removed during life in several cases of recent cholecystitis.

Whether in typhoid fever and in other infectious diseases there may be a stagnation in the bile-current and a vitiation in the quality, as suggested by Harley, that allow the ready invasion of intestinal germs, or whether this may be preceded by a catarrhal cholecystitis engendered by the passage of typhoid bacilli through the portal circulation, cannot be easily determined. Both channels are open. It has been shown experimentally by Pisenti[22] that the amount of bile secreted is diminished from one-half to two-thirds during septic fever in animals, and the same tendency may be assumed to be present in some degree during typhoid fever.

As to infection through the blood-stream, it is held by Sherrington[23] that "though the blood be teeming with micro-organisms none can escape through the normal hepatic tissues, and it is only when the latter have been damaged by toxins in the blood, formed by the life of the bacteria, that the tissues allow the germs to pass through them." Experiments by Blachstein[24] and others showed that, after the intravenous inoculation of animals with the typhoid bacillus, the gall-bladder in numerous instances was infected ten or twelve days later. In two rabbits these organisms were found to be very active in the bile after very long periods—from three to four months.

It is a matter of common observation that the bacilli of typhoid are voided with the urine, which they must reach, according to the observations of Flexner,[25] through the glomerular capillaries, and there appears to be sufficient proof that the hepatic secretion is contaminated in a similar manner through the portal circulation. The suggestion

of Chiari, that germs may pass directly through the intestinal wall to the gall-bladder, cannot be substantiated, although the fecal odor is probably thus imparted.

Therefore we must conclude that infection of the gall-bladder takes place by the passage of micro-organisms through the biliary ducts, with the supplementary agency of a contaminated blood-current.

Relation of Gallstone to Etiology. Recent studies (Naunyn,[21] Courvoisier,[6] Brockbank,[22] Mayo Robson[26]) leave no doubt that gallstones render the biliary ducts and gall-bladder more receptive to infecting microbes, especially if either the common or the cystic duct is obstructed. The presence of calculi in a typhoid-fever patient would undoubtedly favor the occurrence of accidents from severe gall-bladder infection, and this is substantiated by the post-mortem evidence in some of the cases previously cited, since about one-fourth of the patients who died with typhoidal cholecystitis were found to have gallstones. But in the great majority of cases no calculi were present, and no evidences of previous local lesions. Moreover, several were in childhood, more in the adolescent period of life, when gallstones are comparatively rare. Therefore it may be assumed, in view of Chiari's discovery of Eberth's bacillus in the gall-bladder at nearly all his typhoid autopsies, that the pre-existence of gallstones is not an essential feature in the infective process.

Typhoid Infection as a Cause of Gallstones. There is more ground for the supposition that typhoid fever, through gall-bladder infection, may be an important factor in the etiology of gallstones.

Bernheim[27] suggested this sequence, stating that he had seen three or four times veritable accessions of biliary colic in the course of typhoid fever in subjects who had never had such attacks before. "May typhoid fever," he asks, "produce alteration or stagnation of bile, and thus determine the formation of gallstones?"

The prolonged vitality of the typhoid bacillus within the body is well known, and is instanced by the two cases previously cited, in which pure cultures were obtained from the gall-bladder in patients who came to operation for calculous cholecystitis five and eight months respectively after the termination of the fever.

A similar report by Chantemesse[28] relates to a case of grave typhoid with slow convalescence. Six months later, after an interval of perfect health, biliary colic appeared for the first time with icterus from

obstruction. Surgical operation. Gallstones. Pure culture of typhoid bacilli from the gall-bladder.

Especially interesting as bearing upon this point is the communication of Dr. Dufourt,[29] of Vichy, on "The Rôle of Typhoid Fever in the Etiology of Biliary Lithiasis." Nineteen patients with gallstones had their first attacks of colic after severe typhoid fever. These attacks came on as early as the second month after the fever in two cases; in the third month in six cases; in the fourth month in three, and in the fifth month in one; while the remaining five dated their first symptoms at ten months or later after recovery from the fever. Such cases may be classed with the so-called "hepatic typhus" of French writers.[30]

Whether the micro-organisms may cause a chemical precipitate in the gall-bladder from which cholesterin calculi are formed, or whether the bacilli themselves act as nuclei, is a matter for further study; but stagnation of bile, an important factor in stone-formation, may be assumed to be present in typhoid fever. Naunyn states that he has found micro-organisms in the centre of a few bilirubin-calcium calculi, but this is very exceptional.

Reinfection and Relapse. Chiari thinks that the possibility of reinfection through the intestine by bacilli from the gall-bladder should be considered. The occurrence of relapse in typhoid is an arbitrary matter and inexplicable. The belief that it is caused by the resumption of solid food *per se* is untenable. In certain cases the gall-bladder becomes a stagnant reservoir of typhoid bacilli, so to speak, under conditions favorable to prolonged and virulent activity. Therefore it is by no means impossible that an increase of food, by exciting a stronger flow of bile, may send back to the intestine a new growth of organisms, which in turn cause those exacerbations and relapses that are often attributed to errors of diet.

Pathological Changes. The pathological changes that have been noted involve the gall-bladder, the ducts, and the peritoneum. The cholecystitis may be catarrhal, with an exudate which at first is mostly serous. In other cases it is entirely purulent. Ulcers, often multiple, are found chiefly at the fundus, but they may cause perforation at the neck or elsewhere. Abscess involving the wall alone has been observed, and in some instances the gall-bladder is destroyed by gangrenous inflammation.

In many cases the ducts have been free, with little evidence of cholangitis. In others impacted gallstones were found, and jaundice is mentioned not infrequently. It cannot be supposed that great distention of the gall-bladder occurs without obstruction, although this may not be apparent after death, if rupture has taken place. Brockbank[21] states that "the cystic duct is curved like the letter S in its course between the neck of the gall-bladder and its junction with the hepatic duct, and pressure on it from a full gall-bladder, whether the fulness be caused by calculi or fluid only, will, at times, obliterate its lumen and induce further collection of the secretion of the wall of the gall-bladder, with consequent dilatation of the latter."

When this obstruction is the result of pressure or of inflammatory thickening the cystic duct may again become patent. But when the duct becomes impervious and takes "the appearance of a fibrous cord," the lumen is entirely obliterated by adhesive inflammation.

In many of the cases cited it has been noted that the fluid confined within the gall-bladder was pale, semi-serous, of low specific gravity, and lacking the usual appearances and chemical constituents of bile. This change, by which the gall-bladder secretion replaces the bile, goes on somewhat rapidly after the stoppage of the cystic duct.

A localized peritonitis may be induced by contiguity even when there is no perforation; and if rupture occurs later, the escaping fluid may be limited to the right hypochondrium by adhesions between the liver, abdominal wall, and transverse colon.

Clinical and Diagnostic Features. In turning to the clinical aspect of gall-bladder infection it is apparent that, although we must believe that many or most cases of typhoid fever present bacteriological evidence of such infection, the symptoms caused thereby are seldom of importance; but, on the other hand, the inflammation may reach such a degree of severity that life is cut off without warning of the local danger. In more than half the cases recorded, either through the latency of the symptoms, or on account of typhoidal stupor, nothing unusual was observed. Thus the gall-bladder may become distended or perforation may occur without detection.

The subjects are mostly young, and childhood is not exempt from this complication. Several cases under ten years of age have been reported. Those instances in which this condition can be determined during life present fairly diagnostic symptoms. They are: pain in

the region of the gall-bladder and under the scapula; a palpable, very tender swelling that is dull on percussion, sometimes pear-shaped and visible, giving a doubtful fluctuation, described in one instance as like that of a tense hydrocele. "In gall-bladder inflammation," says Mr. Mayo Robson,[32] "there is almost invariably a tender spot a little above and to the right of the umbilicus, or, to be more exact, at the junction of the upper two-thirds with the lower third of a line drawn from the ninth rib to the umbilicus."

If perforation occurs, these symptoms are merged into those of collapse and general or local peritonitis, of which the cause can only be inferred from its manner of development and the previous history.

The conditions to be excluded in diagnosis, in the more latent stages, are impacted feces, hydronephrosis, cyst, displaced kidney, and appendicitis; and, when rupture of the gall-bladder has occurred, intestinal perforation. The distended gall-bladder gives more pain than either of the first three affections. A displaced kidney is movable, and the appendix is seldom found in the right hypochondrium. Collapse and peritonitis from rupture of the gall-bladder, as before mentioned and as observed in numerous cases, may be indistinguishable from these conditions when due to intestinal perforation. Marked leucocytosis would be suggestive.

PROGNOSIS. The prognosis is unfavorable if the gall-bladder has become much distended or if deep ulceration has taken place, unless the symptoms can be promptly relieved. The local dangers in addition to those from the fever itself are very great. Among the cases that I have found reported one-quarter only got well, including those of post-typhoid cholecystotomy in which Eberth's bacilli were discovered at operation. Without doubt many cases of typhoidal cholecystitis recover spontaneously and go unobserved or unrecorded. But it is equally probable that others die in whom this state is unsuspected.

TREATMENT. The indications are, to relieve pain by opiates and local applications, hot or cold; to avert perforation, if possible, by absolute quietude or tapping the gall-bladder; and, if rupture occurs or appears inevitable, to resort to the promptest surgery.

I know of no case similar to mine in which typhoidal cholecystitis, as determined both clinically and bacteriologically at the height of the fever, has required immediate intervention. There may be others.

Fortunately, a simple tapping relieved pressure, opened the cystic duct, and allowed escape for the sero-purulent fluid.

Had reaccumulation occurred, in the absence of peritonitis, expectant measures or tapping again would have been indicated, as the acute typhoidal state is a very unfavorable one for radical surgery.

In case of perforation and septic peritonitis, however, laparotomy should be performed as affording almost the only chance; but probably a better one than after intestinal perforation at the same stage of typhoid fever, because the inflammatory processes *may* be limited to the right hypochondrium, and the gall-bladder is a less vital part.

Such operations will be rare; but if done in the declining stage of the fever or during convalescence, the prospect of success is less unfavorable. A case of this kind, thus far the only one, I believe, was reported in the *Lancet* two years ago by Mr. Monier-Williams and Mr. Sheild:[33]

Case. A female, thirty-one years old, on the eleventh day of typhoid fever had sudden, severe abdominal pain with semi-collapse. The pain was limited to the upper half of the abdomen, and was thought to be due to an intestinal perforation. The patient recovered from this complication and became convalescent in the fourth week. The temperature was normal for a fortnight, when, at the end of the sixth week, there was another sudden, severe accession of pain and tenderness in the right hypochondrium at the hepatic flexure of the colon. Here a dull tumor appeared—the size of an orange. Again a diagnosis of probable intestinal perforation was made, and the condition was regarded as nearly hopeless. The next day there was slight rallying from collapse and a worse abdominal condition. Operation was decided upon. Median incision, extended later to the right, showed turbid fluid in the right hypochondriac region chiefly, but no perforation of the intestine. The gall-bladder was deeply inflamed, of a dark plum color, thickened, adherent, and tightly distended. Near the neck was an ulcer, the size of a threepenny piece, with a small perforation, through which oozed the contents. The gall-bladder was opened and emptied of an ounce and a half of thick, offensive pus. There were no calculi. The patient made a good recovery. No satisfactory bacteriological examination was made.

Conclusions. From this study the following conclusions are drawn:

1. The gall-bladder in typhoid fever is often infected by Eberth's bacillus; seldom by other organisms (streptococcus; bacillus coli communis).[34]

2. Fatal cholecystitis may result, the inflammation often involving

the ducts (cholangitis), less frequently the hepatic parenchyma (abscess).

3. Gallstones predispose to this complication; and, on the other hand, there is ground for thinking that typhoid fever may determine the formation of calculi in predisposed subjects.

4. The gall-bladder may be a focus for systemic reinfection.

5. Diagnostic symptoms sometimes indicate the necessity for evacuating the gall-bladder by tapping or cholecystotomy.

ILLUSTRATIVE CASES.

1. *Case, with recovery.* Leudet (Hagenmüller, *op. cit.*). Female, thirty-six years. Fourth week, pyriform tumor in right hypochondrium, disappearing in ten days; reappearing at intervals during seven weeks. No jaundice. Recovery.

2. *Case, with recovery.* Griesinger (Hagenmüller, *op. cit.*). Female, aged twenty years. Sixth week, peritonitis, slight icterus. Painful tumor to right of umbilicus. Swelling of liver; collapse; convalescence. In eighth week sudden return of tumor, with chills, icterus, vomiting; later, two more relapses. Recovery fifth month.

3. *Case, with recovery.* Laveran (Hagenmüller, *op cit.*). Man, aged twenty-three years. Painful symptoms and tumor in region of gall-bladder in sixth week. Recovery.

4. *Case.* Martin-Solon (*Bull. Fac. de Méd. de Paris*, 1820–'21, vii. pp. 370–375). Patient died of peritonitis, and twenty-five ulcers of gall-bladder were found. Previous illness not clearly typhoid fever. *Enterite* (?).

5. *Case.* Husson (*Bull. de la Soc. Anat.*, 1893, p. 104). Child, aged eight years. Died at end of third week. Perforated gall-bladder. Cystic duct obliterated and converted into fibrous cord.

6. *Case.* Dumoulin (*Gaz. Méd. de Paris*, 1884, 3d series, tome iii. p. 551). Man, aged nineteen years. Third week, constant nausea and vomiting. Enormous tumor in right hypochrondrium, extending to left of umbilicus and into right iliac fossa. Resistance like tense hydrocele. Liver raised. Upper limit line of right nipple. Diagnosis: distended gall-bladder. Repeated chills, suggestive of hepatic abscess. Coma; death, sixteenth day. Autopsy: typical intestinal lesions of typhoid; tumor, size of head, containing two litres of greenish bile; no gallstones; adhesions with liver, transverse colon, etc.

7. *Case.* Archambault (*Bull. de la Soc. Anat.*, 1852, p. 90). Infant. Thirtieth day, signs of intestinal perforation. Death twelve days later. Perforation of gall-bladder; localized peritonitis.

8. *Case.* Barthez and Rilliet (*Maladies des Enfants*, second edition, 1853, vol. ii. pp. 5, 701). Girl, aged twelve years. Sixteenth day, tumor in right hypochondrium, that gradually disappeared. Death, fifty-second day. Autopsy: perforated gall-bladder; circumscribed pus cavity between liver, stomach, gall-bladder, and colon.

9. *Case.* Ranvier (*Bull. de la Soc. Anat. de Paris*, 2 S., tome viii., 1863, p. 432). Man, aged twenty-eight years. Died during convalescence in the fifth week. Autopsy: limited peritonitis; perforated gall-bladder; right side of abdomen filled with yellowish, opaque liquid. Walls of gall bladder two or three millimeters thick and infiltrated with pus. A small calculus. Peyer's patches in stage of cicatrization. Author says he cannot explain this point of suppurative election, *si bizarre.*

10. *Case.* L. Colin (*Études clin. de mêd. militaire*, p. 197, Paris, 1864). Soldier; end of third week of rather mild attack; jaundice, gastro-abdominal pain. Death eleven days later. Autopsy: peritonitis limited by transverse colon, liver, and abdominal wall. Gall-bladder size of goose-egg; perforated. No gallstones. Ducts pervious. Typical intestinal lesions.

11. *Case.* C. E. E. Hoffmann ("Zerstörung der Gallenblase bei Typhus," Virchow's *Archiv*, 1868, xlii. 219–222). Female, aged twenty-five years; jaundice sixth week; eighth week sinuses discharging through abdominal wall. Death twelfth week. Autopsy: destruction of gall-bladder. Abscess beneath liver containing twelve gallstones. Lesions of typhoid.

12. *Case.* Foot, O. W. ("Enteric Fever. Abscess in Walls of Gall-bladder," *Irish Hosp. Gaz.*, Dublin, 1874, ii.). Female, aged thirty-two years. Died in eighth week. Small abscess between coats of gall-bladder communicating by a narrow orifice with interior. Extensive adhesions of abdominal wall. One cholesterin calculus, twenty-three grains.

13. *Case.* Burger ("Typhus abdom. mit Perforat. der Gallenblase in die Bursa Omentalis," *Deutsches Archiv. für klin. Med.*, Leipzig, 1873–'74, xii. S. 623–630). Man, aged forty-one years. Twelfth day, pain and tumor size of apple in region of gall-bladder; gradual increase in size; chills; no jaundice. Death from peritonitis in fifth week. Perforation of gall-bladder. Adhesions forming cavity filled with pus. No gallstones; no abscess of liver.

14. *Case.* P. L. Legendre (*Bull. de la Soc. Anat. de Paris*, fourth series, tome vi., 1881, p. 193). Female, aged thirty years. In second week peritonitis at right upper abdomen. Death twelve days later. Autopsy: perforation of gall-bladder. Pus in peritoneal cavity. Three gallstones.

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DISCUSSION.

DR. WILLIAM T. COUNCILMAN: As regards the frequency with which the typhoid bacillus may be found in the gall-bladder, I think that the experience I have had with the disease would tend to show that the bacillus is found in nearly every case, certainly as frequently as it was found by Chiari. I have come to regard the gall-bladder as one of the surest places to obtain a pure culture of the organism. As to the manner of infection, I think that it enters the gall-bladder through the blood. In every case of typhoid a few bacilli enter into the blood. The conditions of the circulation in the liver render it most likely that these should be retained there. From the bloodvessels of the liver they can enter into the biliary passages through

the foci of necrosis constantly present. Gall-bladder infection is not due to a process of excretion of the organisms by the liver. I have had three cases in which ulcers, similar to the ulcers of the intestine found in typhoid, were found in the gall-bladder.

In connection with this subject I would like to pass around this specimen, showing the focal necrosis in the liver in a case of scarlet fever. The preparation has been made by the Kaiserling method. The necrotic foci are more apparent than they ever are in typhoid fever.

UREA ESTIMATIONS IN CASES OF TYPHOID FEVER TREATED BY THE BRAND BATH METHOD.

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E. B. C., a bookkeeper, aged 25, was admitted to the hospital of the University of Pennsylvania, December 25, 1896. His family and personal history had no bearing on his existing illness, which began apparently on the 17th of December with a severe backache. He had headache also two days earlier, but this disappeared and did not return. On the 24th, the day before admission, diarrhœa set in, he having previously been constipated. On this day too (the 24th) he had a small epistaxis. There had been some cough for several weeks. On admission, at 3.30 P.M., his temperature was 102.8° F. At 8.30 in the evening it was 103.8° F. His tongue was slightly coated, but not dry; his belly somewhat distended. The spleen was decidedly enlarged, but there were no rose-colored spots on that day. These were unmistakably present on the 28th. On the day of admission the urine was examined and a small albuminuria found. To this were added, on the 27th, hyaline casts. The diagnosis of typhoid fever seeming sufficiently justified, tubbing at 102.2° F. was commenced on the 27th. The effect upon the temperature was prompt, lowering it from 104.4° F. to 98.4° F., at the fourth bath, received at 11.45 of the 28th. On this day a copious purulent expectoration, tenacious and bloody, was noted, containing also numerous diplococci; but the physical signs of a croupous pneumonia could not be elicited. The albuminuria on this day had increased to one-fourth bulk, and hyaline casts were numerous.

We were not deterred from tubbing by these symptoms, though the bronchitis was deep-seated. Indeed, there was probably a broncho-pneumonia. It was thought that this would be a suitable case on which to make a study of the urine. The diet was the usual liquid diet of typhoid fever, wholly milk.

We began to collect the urine on the 29th, when but eleven ounces and a half were gathered, representing a part only of the twenty-four hours' quantity. This contained 2.9 per cent of urea. The daily amount was measured and the urea estimated daily for a month succeeding, until convalescence was thoroughly established. The results are:

	Quantity.		*Urea.*	
December 30, 1896,	24 oz. (720 c.c.)	2.52 per cent.	18.82+ gms.	(288.72 grains.)
" 31, "	40 " (1200 ")	2.65 "	32.11+ "	(495.60 ")
January 1, 1897,	48 " (1440 ")	2.14 "	20.46+ "	(480.00 ")
" 2, "	66 " (1980 ")	1.64 "	32.80+ "	(506.22 ")
" 3, "	56 " (1680 ")	1.89 "	31.98+ "	(494.43 ")
" 4, "	60 " (1800 ")	1.77 "	32.16+ "	(496 20 ")
" 5, "	45 " (1350 ")	1.77 "	24.76+ "	(382.15 ")
" 6, "	44 " (1320 ")	2.14 "	28.61+ "	(440.00 ")
" 7, "	52 " (1560 ")	1.64 "	25.84+ "	(398.84 ")
" 8, "	32 " (960 ")	1.51 "	14.57+ "	(225.98 ")
" 9, "	48 " (1440 ")	1.89 "	27.33+ "	(421.84 ")
" 10, "	48 " (1440 ")	1.51 "	21.96+ "	(338.88 ")
" 11, "	68 " (2040 ")	2.14 "	44.07+ "	(680.00 ")
" 12, "	40 " (1200 ")	2.52 "	30.58+ "	(471.20 ")
" 13, "	38 " (1140 ")	2.14 "	24.62+ "	(380.00 ")
" 14, "	62 " (1860 ")	1.89 "	35.48+ "	(547.46 ")
" 15, "	44 " (1320 ")	2.52 "	33.59+ "	(518.32 ")
" 16, "	64 " (1940 ")	1.89 "	36.49+ "	(563.12 ")
" 17, "	42 " (1260 ")	1.64 "	20.81+ "	(321.14 ")
" 18, "	48 " (1440 ")	1.64 "	23.86+ "	(368.16 ")
" 19, "	48 " (1440 ")	1.64 "	23.86+ "	(368.16 ")
" 20, "	56 " (1680 ")	1.89 "	31.98+ "	(494.48 ")
" 21, "	68 " (2040 ")	1.51 "	31.11+ "	(480.08 ")
" 22, "	66 " (2080 ")	1.51 "	30.45+ "	(465.96 ")
" 23, "	30 " (900 ")	1.39+ "	12.63+ "	(195.99 ")
" 24, "	42 " (1260 ")	1.64 "	13.03+ "	(201.00 ")
" 25, "	70 " (2100 ")	1.51 "	29.87+ "	(460.92 ")
" 26, "	70 " (2100 ")	1.39 "	24.76+ "	(382.15 ")
" 27, "	76 " (2280 ")	1.51 "	32.11+ "	(495.60 ")
" 28, "	76 " (2280 ")	1.51 "	32.11+ "	(495 60 ")

Albumin.	*Albumin.*
December 29, 1896, a one-quarter bulk.	January 4, 1897, a one-tenth bulk.
" 30, " " " " "	" 5, " " one-twelfth "
" 31, " " " " "	" 6, " " trace.
January 1, 1897, " " " "	" 7 to 19, " " "
" 2, " " one-fifth "	" 24, " None.
" 3, " " " " "	

Thus it will be seen that so far from there being a suppression of urine during the baths the secretion was markedly increased, amounting to 1980 c.c. (66 + oz.) in the twenty-four hours on January 2d, when he was tubbed five times. In the corresponding twenty-four hours the urea reached 32.8 gms. (506.2 grains), and this, too, on a milk diet, which affords a moderate percentage of proteids. On the 3d there were 1680 c.c. (56 ounces) and 31.98 gms. (494.4 grains) of urea; on the 4th, 1800 c.c. (60 ounces) with 32.16 gms. (496.2 grains). Then followed a few days of smaller but still free secretion until the 11th, when 2040 c.c. (68 ounces) were again recorded. Throughout the remainder of the illness the secretion, as will be seen from the table, was liberal but fluctuating. He had his last bath, the fifty-third, on the 12th of January. On the 11th, when two baths were given, the urine rose to 2040 c.c. (68 ounces), with the urea at 44.07 gms. (680 grains), the maximum attained while the analyses were being made. On the twenty-fifth,

twenty-sixth, twenty-seventh, and twenty-eighth days of the disease the quantities were 2100 c.c. (70 ounces), 2100 c.c. (70 ounces), 2280 c.c. (76 ounces), 2280 c.c. (76 ounces), with urea amounting to 29.87 gms. (460.9 grains), 24.76 gms. (382 grains), 32.11 gms. (495.6 grains), 32.11 gms. (495.6 grains).

The albumin remained at one-quarter bulk until January 2d, when it fell to one-fifth. On the 5th of January it was one-twelfth bulk. After that date it disappeared and with it the casts.

No treatment was ordered for the cough, and on the 4th of January the notes inform us that it continued, though showing some abatement, the expectoration being still copious and muco-purulent, sometimes bloody. On the 7th, we noted that his cough was less, but expectoration about the same. On this day the sputum was examined for tubercle bacilli with negative results. By the 18th the cough had abated greatly, though the expectoration still contained some blood. Its exact source is not known. At the date of his discharge, February 12th, the cough and expectoration had completely disappeared. A physical examination on the day previous failed to discover anything abnormal.

On January 12th we noted "the patient has developed an otitis media," and on the 18th "both ears are noted as discharging;" on the 20th "that he is deaf," but in other respects is doing well. There appeared no defect in his hearing at the date of discharge.

This is the history of a case of typhoid fever strikingly complicated with conditions which superficial observation would expect to increase any risk to which the patient is subjected by cold bathing, viz., nephritis and deep-seated bronchitis, possibly broncho-pneumonia. So far from aggravating either of these two conditions, both abated and early disappeared. The urine, so far from falling off, increased in quantity, and the urea elimination rose, *pari passu*.

The nephritis was, of course, mild, and it is not likely that the kidney lesion amounted to more than cloudy swelling of the cells. Whether a more active inflammatory condition of the kidney would justify continuing the baths is not so simple a question. Our associate, Dr. Charles G. Stockton, in his part of the splendid symposium held at the annual meeting of the Medical Society of New York, at Albany, on January 28, 1897, "On the Relation of Impure Water to Disease, and the Cure and Prevention of the Latter," names renal complications and intestinal hemorrhage as the only two conditions which contraindicate the full method of Brand. By renal complications he specifically states he means actual inflammatory involvement of the renal epithelium, and probably did not intend the simpler condition of cloudy swelling probably present in my case. In point of

fact, such a positive degree of inflammation is rarely met in typhoid fever, but I am inclined to think I would not be deterred from using the tub treatment by the presence of any degree of nephritis, provided the conditions otherwise calling for it were present. For, after all, in inflammation of the kidney it is not the rapid movement of the blood through the organ which constitutes the inflammation, but rather its stagnation. Now the direct effect of cold is to increase the force of the heart's contraction, to impel the blood onward, and carry it and its toxic ingredients through the kidney, in the course of which a large proportion of these toxic matters are excreted with the urine. E. Ausset[1] has shown conclusively that the toxic properties of the urine secreted during the baths is increased, as contrasted with the urine in cases of typhoid not tubbed. Indeed he assigns almost the entire efficiency of the Brand treatment to this active elimination of toxic agencies.

Vogel's experience supports my own notion as to the harmlessness of the baths, even if active nephritis is present. He refers to an epidemic of scarlet fever among soldiers, a part of whom, on account of circumstances, were treated on the expectant plan and a part with cold baths at 68° to 72° F. every three hours, when the rectal temperature reached 102.2°. Of the 69 patients subjected to the cold bath treatment 5 had nephritis, of whom none died. Of 56 treated by the expectant plan 9 had nephritis and 5 died.

The effect of cold baths in exciting secretion of urine has long been recognized, and almost every person who is in the habit of taking a frequent cold bath has experienced such effect in his own person. It is not remarkable, however, therefore, that diureses should be a constant event of the Brand method of treating typhoid fever. The earliest observers of the Brand method called attention to this fact, and every one who has watched the effect of the treatment confirms this. As many as 4000 and 5000 cubic centimetres have been noted.

I have not as yet met the results of systematic urea estimations daily carried out in the study of the effects of this treatment. The sources of urea in the urine in fever are two: first, the nitrogen in the proteid food ingested; second, the oxidation of tissue, which is much increased during the fever-process. It is comparatively easy

[1] E. Ausset: Bulletins et Mémoires de la Société Médicale des Hopitaux de Paris. Tome ii. 3 serie, 1894, p. 825.

to estimate the nitrogen ingested by my patient. Being on a milk-diet throughout the whole period of observation, six ounces every two hours or seventy-two ounces in the twenty-four, the daily amount of milk may be put down at 2232 grammes. Allowing 600 milligrammes of nitrogen for each 100 grammes of milk, the approximate daily amount of nitrogen would be 13,382 grammes. Of the total nitrogen elimination 95 per cent. may be approximately assigned to the urine and 5 per cent. to feces, whence 12.7 grammes would be eliminated. Of this, however, 10 per cent. is uric-acid nitrogen and 85 per cent. or 11 grammes urea nitrogen. Finally, since the ratio of urea to nitrogen is as 60 : 28, the proper amount of urea derived from food ingestion would be about twenty-four grammes if all the milk ingested were absorbed. In point of fact, the actual amount absorbed is probably considerably less than is ingested, so that the urea should be correspondingly less. The urea arising from tissue metamorphosis is of course disregarded, but allowing for this the results of my analyses show that the kidneys are quite equal to the work demanded of them. It would be more satisfactory to compare these results with analyses of the urine of a case of typhoid fever on a like diet not treated by the baths. At present my confidence in the hydriatic treatment is such that I would not feel comfortable to treat a case in any other way unless such treatment were insisted upon by the patient.

THE INFLAMMATIONS OF THE COLON.

By FRANCIS DELAFIELD, M.D.,
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THE descriptions of dysentery to be found in books, and the ideas concerning dysentery which exist in the minds of physicians, are derived largely from the consideration of four sets of cases: The severe and often fatal dysentery of tropical countries; the dysentery which has always accompanied armies; the mild catarrhal dysentery of temperate climates, and the more recently described amœbic dysentery. For those of us who live and practise in temperate climates something more is required. There are a number of points concerning which we need the teachings of local experience. The causation, lesions, prognosis, and treatment of inflammations of the colon as they occur in ordinary practice in temperate climates have not yet been studied in sufficient detail.

The present paper is an attempt to describe the different forms of colitis which are ordinarily seen in the city of New York and its suburbs.

In New York, while the disease is not at most times very prevalent, yet the variety of cases is considerable, so that in the course of years one may see a number of cases of inflammation of the colon which differ widely from each other as regards their lesions, symptoms, prognosis, and treatment.

1. The most common of all the forms of colitis and the one with which every physician is familiar is that in which there are no structural changes in the wall of the colon—nothing but congestion, an increased production of mucus, and an exudation of serum. It is usually called acute catarrhal colitis, or acute catarrhal dysentery.

For practical purposes it is necessary to divide this class of cases into two varieties: one characterized by the increased production of mucus, and the other by the increased exudation of serum.

We will speak first, therefore, of (*a*) colitis, with an increased production of mucus.

Lesions. As this form of colitis is rarely fatal in adults, our knowledge of the lesions is derived from it as it occurs in children, as it is associated with other forms of colitis, as it is produced experimentally in animals, and, from the character of the discharges, from the bowels during life. The inflammation begins regularly in the rectum, and either remains confined to this part of the colon or extends upward, but in children a large part of the colon and the lower end of the ileum may be inflamed from the first. The glandular and connective tissue coats are swollen and congested, and more or less infiltrated with serum and a few leucocytes. There is an increased production of mucus, which coats the inner surface of the colon and is passed by the patient. There is often a moderate bleeding from the surface of the inflamed mucous membrane. The epithelial cells which line the glandular tubules are distended with mucus, and the superficial cells desquamate and are mixed with the mucus. The solitary lymph nodes in the wall of the intestine are often swollen; in children there may be a considerable infiltration of the glandular coat with pus-cells and necrosis of the swollen lymph nodes.

Etiology. It must be admitted that, although this form of colitis occurs very frequently, we have no satisfactory knowledge of its causation. A variety of bacteria have been found in the passages, but no one of them can be considered as a certain cause of the inflammation. The most definite causes are: impure drinking-water and impure milk, but unripe or decayed fruits and vegetables seem also to act as irritants. The liability to such a colitis is apparently much heightened by a continual high temperature of the air, and by the crowding of people together.

Symptoms. If the inflammation is confined to the lower end of the colon, it regularly runs its course within a week, and the patients recover. The principal symptoms are the local ones—pain in the rectum, an irritability of its mucous membrane which makes it try to discharge everything in contact with it, and the frequent passage of small quantities of blood and mucus. Although the passages of blood and mucus are frequent, but little fecal matter comes away with them. Besides the local symptoms there is a moderate rise of

temperature, with more or less prostration. Some of the patients do not go to bed; some do not even stop work.

If, however, the inflammation not only involves the rectum, but extends up into the colon, the patients are more seriously ill, especially if they are young children. The quantity of mucus discharged from the bowels is considerable, and very little fecal matter may be passed for one or two weeks. As the inflammation subsides the quantity of mucus decreases and the quantity of fecal matter increases. In these patients the temperature is higher, the duration of the disease longer, and the prostration greater. Adults regularly recover, but children often die.

Treatment. The disease is to be looked for during the summer and autumn months, and it is during those months that special care is to be exercised against the ingestion of impure water and milk, unripe and decayed fruit and vegetables, and indigestible articles of food.

Of the colitis itself the essential parts of the treatment are rest in bed, a fluid diet, the emptying of the colon by castor-oil or sulphate of magnesia, and the relief of pain by small doses of some preparation of opium. In most of the cases very prompt relief is given by the daily irrigation of the rectum with a quart of a weak infusion of flaxseed. Such an acute colitis is sometimes followed by a chronic inflammatory process which may continue for years. The chronic colitis follows one of two types.

(1) The excessive production of mucus continues, the connective tissue and muscular coat become thickened, the glandular coat is more or less irregularly thickened or thinned, the patients continue to have frequent passages of mucus, fluid feces, and sometimes blood. They lose flesh and strength as long as the colitis continues. The treatment of these patients is difficult, and many of them do not recover.

(2) The excessive production of mucus continues. There are no anatomical changes in the wall of the colon. The feces are sometimes formed, sometimes fluid. Mucus is passed by itself and as a coating of the formed feces. The patients suffer from more or less pain, nervous disturbances, and loss of nutrition, but their condition is not a very serious one. The treatment is often difficult, especially on account of the nervous disturbances, but many of the

patients can be cured. This condition is not to be confounded with the so-called "membranous enteritis."

(*b*) Acute colitis with a large exudation of serum.

These cases are not to be confounded with the cases which I have described elsewhere under the name of "Morning Diarrhœa." The condition is an inflammatory one, and not a functional disturbance.

Lesions. The disease is not a fatal one, and I have never had the opportunity of seeing the colon of one of the patients. The character of the symptoms is such as to make one believe that the inflammation involves the upper part of the colon, and that the exudation of serum into the cavity of the gut is the principal feature of the morbid process.

Etiology. This form of colitis is specially common when, during the summer, there is a week of continuous hot weather. Cases, however, are seen at all times of the year. How far drinking-water, or milk, or food may be responsible for an attack it is difficult to say. In some persons there is a well-marked predisposition to this form of colitis, so that they suffer from a number of attacks.

Symptoms. The patients have at first a feeling of discomfort in the abdomen, or colicky pains, moderate prostration, and sometimes nausea. Then there is the feeling of the necessity for emptying the bowel. The patients go to the water-closet, sit down, the sphincter opens, and a large quantity of fluid runs out without any effort at expulsion. The fluid consists of fluid feces, serum, and mucus. The quantity of each discharge is considerable, sometimes as much as two quarts. There are a number of such discharges during each twenty-four hours. The patients are not always confined to bed, but they are weak and miserable. As a rule, there is no febrile movement. Such an attack may only last for a few days, or it may continue for weeks or months.

Treatment. A large number of the cases get well under a variety of treatments, or even without any medication at all. But, on the other hand, there is a considerable number of cases in which the disease continues in spite of treatment. Every year I see several patients in whom the colitis has continued for months in spite of treatment by diet, opium, bismuth, and the intestinal antiseptics. The best plan for the management of these patients is this: a milk diet, except for one solid meal a day, one-fourth of a grain of codeia

after each movement of the bowels, and five minims of castor-oil with five grains of salol to be taken together four times a day.

2. There is a form of colitis of which the most marked anatomical feature is the infiltration of the connective tissue coat of the colon with pus-cells. This infiltration is a large one, so that the wall of the colon is irregularly thickened. The glandular coat is also infiltrated with pus, but to a much less extent. I have only seen a few cases of this form of colitis, so that I cannot give a complete account of it. The inflammation involves the upper rather than the lower part of the colon. The passages are diarrhœal and not dysenteric. The patients look as if they were suffering from septic poisoning. It seems evident that the process is not a severe catarrhal inflammation, but a primary infection of the connective tissue coat. The disease may prove fatal within a few days, or may continue for as long as a year. Treatment is altogether unsatisfactory.

3. There is a form of colitis to which I wish to call special attention, because it is one of the most important forms of the disease that we have to deal with in New York.

Lesions. The anatomical characters of this form of colitis are an increased production of mucus, an exudation of serum, an emigration of white blood-cells, a growth of new connective tissue in the glandular coat and the connective tissue coat, and small areas of necrosis of the glandular coat.

The inflammation prefers the upper part of the colon, but it may involve its entire length or be confined to its lower third.

The gross appearance of the colon is that of congestion of the mucous membrane with perhaps a coating of mucus—the ordinary appearance of an acute catarrhal inflammation. But if we look more closely, we see that in addition there are numerous small, superficial ulcers, many of them so small that they cannot be seen with the naked eye. In the old and severe cases, however, instead of these small ulcers we find a destruction of large areas of the glandular coat.

The morbid changes belong to the glandular coat, but may extend to the superficial layers of the connective tissue coat. The destruction of the glandular coat is effected by simple necrosis, or by an infiltration with pus-cells. The ulcers do not have overhanging edges. Between the ulcers some of the tubules show necrosis of their

epithelium, while some are obliterated by the growth of cells between them The tissue between the tubules is thickened by a growth of connective-tissue cells or by an infiltration with pus-cells, or by both. There may also be a moderate infiltration of the superficial layers of the connective tissue coat, with pus-cells and connective tissue cells.

Etiology. I have never been able to make out the causation of this form of colitis. It is not infrequent in New York. It is seen both in hospital and private practice. It occurs at all seasons of the year. Whether it is caused by impure water, milk, or food, I do not know. The feces show the usual variety of micro-organisms, but the general features of the disease are those of a streptococcus infection.

Symptoms. The invasion of the disease is sudden or gradual. If it is sudden, the patients are attacked with vomiting, frequent passages, abdominal pain, prostration, and a rise in temperature. The first passages are diarrhœal—large, and composed of fecal matter, serum, and mucus ; or dysenteric—small, painful, and composed of mucus and blood. The dysenteric passages do not continue ; they belong to the first days of the disease. The prostration is considerable, the patients look sicker than they do with an ordinary catarrhal colitis. Sometimes there is even a sort of shock given by the invasion of the disease ; the patients may have attacks of syncope.

If the invasion is gradual, the patients begin with what seems to be an ordinary diarrhœa, three to five loose, fecal movements a day, with more or less colicky pain, or constant abdominal pain. There is at first no rise of temperature. The patients gradually lose flesh and strength, but it may be several weeks before they go to bed. And yet it is a matter of much importance that the character of the colitis should be recognized and the patients put to bed during this early stage of the disease.

As the disease goes on the passages continue to be frequent and of considerable size. They are composed of fluid feces, serum, mucus, and often blood. The mucus is present in considerable quantities ; it is diffuse, not in the form of nodules. If the patients improve, the fecal matter increases in quantity and becomes more consistent, while the quantity of serum, mucus, and blood dimin-

ishes. The abdominal pain, whether colicky or constant, continues. There is no appetite. In some cases nausea and vomiting are very troublesome symptoms. There is usually a rise of temperature in the afternoon, even in the chronic cases. The patients steadily lose flesh and strength. Of the cases which recover some run their course within four weeks and recover entirely, and yet while the disease is going on the patients are sick enough to cause much anxiety. But there is a considerable proportion of cases in which the disease continues for months before the patients get entirely well. And, finally, there are patients who are under observation for years, who often seem almost well, but yet always relapse.

In the fatal cases I have seen the disease prove fatal in seven days, but that was in a person already exhausted by privation and exposure. The rule is that the disease continues for a number of months before the patients die. Occasionally we see such a colitis in its earlier stages in persons who die from pneumonia.

The prognosis is serious. A moderate number die from the disease, and in a very considerable number the disease is protracted for months.

Treatment. The most important time for the treatment for this form of colitis is during the earlier days of the disease. It is in the patients who are neglected at first that we see the protracted forms of the disease.

No matter how mild the invasion of the disease is the patients should at once be put to bed and on a diet composed principally of milk, and this management must be kept up until all evidences of acute inflammation have disappeared. In the chronic cases, on the other hand, it is important that the patients should get out of doors, and eat a sufficient quantity and variety of food. As a rule, these patients do best in a dry, elevated, inland climate.

During the earlier stages of the disease irrigations of the rectum are of service, and even in the chronic cases such irrigations may be used with advantage from time to time.

As regards medication, it has seemed to me that I obtained the best results both in the acute and chronic cases by the use of combinations of opium, salol, and castor-oil. But I must admit that these remedies sometimes fail and that I see patients recover under other plans of treatment. In the chronic cases the patients are apt

to take, in the course of the disease, a considerable number of drugs. For example, a patient who was sick for eleven months, and was successively under the care of four different physicians, received the following drugs: salol, castor-oil, tincture of opium, dilute sulphuric acid, Blaud's pills, sulphate of morphine, subnitrate of bismuth, sulphate of strychnine, subcarbonate of bismuth, salicylic acid, nitrate of silver, resin of turpentine, salicylate of bismuth, naphthalin, sulphate of quinine, ichthyol, sulphide of calcium, liquor potassæ, codeia, acetate of lead and opium, dilute nitric acid, carbonate of guaiacol, bone marrow, Fowler's solution of arsenic, tincture of cubebs, tincture of hyoscyamus, phenacetin, acetanilid, biniodide of mercury, iodide of potassium. He also received enemata of starch and laudanum, and of corrosive sublimate 1 : 10,000. The man went quietly on with from three to five passages a day, composed of fluid feces, mucus, and sometimes blood, with an afternoon temperature between 100° and 103° F., with progressive loss of flesh and strength. During the tenth month of his illness the afternoon temperatures became lower and the man began to gain flesh and strength. After this the blood and mucus gradually disappeared from the passages, and finally, at the end of the eleventh month, he seemed to be well.

4. There is a form of colitis characterized by the combination of an exudation from the bloodvessels, which forms fibrin, and of necrosis. This is commonly called croupous or diphtheritic dysentery.

The inflammation regularly begins in the rectum. It may remain confined to this part of the colon, or it may extend upward and involve the whole length of the colon and even the lower part of the small intestine.

The irritants which cause the colitis seem to act, according to their virulence, upon the glandular coat alone, or upon the connective tissue coat also, or upon the whole thickness of the wall of the colon.

In the majority of cases the inflammatory changes are produced, not uniformly, but in patches. In the milder cases, therefore, we find the inner surface of the colon studded here and there with little patches of false membrane. Vertical sections of the wall of the colon at these points show a layer of fibrin and pus, necrosis of the superficial portions of the glandular coat, and a little infiltration of

the glandular coat with fibrin and pus. In the more severe cases the layer of fibrin on the inner surface of the colon is thicker, large infiltrations of fibrin are found in the connective tissue coat, and even the muscular and peritoneal coats are involved in the exudation. The necrosis involves the whole thickness of the glandular coat, often extends into the connective tissue coat, and may involve the whole thickness of the wall of the colon. The dead tissue soon sloughs away and leaves ulcers of varying number, size, and depth.

Etiology. In New York this form of colitis belongs to the autumn months, not infrequently people bringing it back to town with them from the country. In such people there may be a history of contaminated drinking-water. The behavior of the inflammation is that of one caused by the presence of pathogenic bacteria, and such bacteria can often be demonstrated in the feces and in the wall of the colon. But it is not to be forgotten that identical anatomical changes are produced by poisoning with corrosive sublimate, so that it is possible that such a colitis may be produced by other irritants than bacteritic toxins.

Symptoms. The patients have numerous small, painful passages of blood and mucus. If the inflammation extends above the rectum, they also pass large quantities of brownish fluid. There is nearly constant rectal pain, irritability, and tenesmus. There may also be colicky pains and strangury. Many of the patients vomit, especially at the beginning of the disease. There is regularly a well-marked febrile movement throughout the disease, but in some of the bad cases the temperature is low throughout. In the severe cases the prostration is marked, the heart's action is rapid and feeble, delirium and stupor are developed. The disease lasts from one to six weeks.

The prognosis is serious on account of the severe character of the lesion, the general poisoning of the patient, and the permanent changes left in the wall of the intestine. If the whole length of the colon is involved, the patients rarely get well. If the ulcers are large and deep, although the patient recovers from the inflammation, he is left with a colon so badly damaged that he is always an invalid.

Treatment. All the patients are to be put to bed and kept on a fluid diet. Most of them require some preparation of opium to keep them comfortable. Many of them need alcoholic stimulants.

It is important to distinguish whether the inflammation is confined to the rectum, or whether it extends higher up. If it is confined to the rectum, it can be treated by irrigation alone; if it involves a large part of the colon, drugs must be given in addition to the irrigation. Two quarts of an aqueous solution of corrosive sublimate, 1 : 10,000, have given me the best results as an irrigation. Ipecac in 20-grain doses once or twice a day seems to be the most efficient drug. I have also seen good results, however, from the use of salol, naphthalin, castor-oil, and nitrate of silver.

5. There is a form of colitis in which the characteristic necrotic and inflammatory changes seem to be due to an infection with the amœba coli.

Lesions. I have examined the colon in eleven fatal cases. In all but one the entire length of the colon was involved, in that one only the upper two-thirds.

The main infection with the amœbæ is in the connective tissue coat, and it is in this coat that the morbid changes begin. The amœbæ seem to cause swelling and necrosis, while other inflammatory changes may be caused by an additional infection with streptococci or other bacteria. The exact method of the necrosis varies somewhat, and several different forms may be present in the same colon.

(*a*) The necrosis may be confined to the glandular coat; there is swelling of the intertubular tissue, and death of the tubules. In this way considerable portions of the glandular coat are destroyed and the connective tissue coat laid bare. At the same time there is a growth of large and small cells in the connective tissue coat.

(*b*) There are circumscribed thickenings of the connective tissue coat, which soon become necrotic. In this way the glandular coat is undermined and ulcers with overhanging edges are formed of varying size and depth.

(*c*) Large portions of the whole thickness of the wall of the colon are swollen and completely necrotic. The patients usually do not live long enough for these dead portions to slough away.

In four of the cases there were amœbic abscesses in the liver. In one case there were amœbic abscesses in the lower lobe of the left lung.

Etiology. It is not easy to determine how persons become in-

fected with amœbæ in New York, where the drinking-water all comes from the same source. Most of the patients had been living in the city for several years.

Symptoms. The invasion of the symptoms is either acute or gradual.

In the acute cases the patient is suddenly attacked with colicky pains and diarrhœa, often with nausea and vomiting, and sometimes a rise in temperature. The stools are frequent, fluid, and sooner or later contain blood and mucus. The quantity of blood may be considerable.

In the more gradual invasion there is at first nothing but a painless diarrhœa—several loose, fecal stools in the twenty-four hours.

The patients have no appetite, they lose flesh and strength, and become anæmic. In some of them the symptoms are continuous, in others there are remissions and exacerbations. Although the temperature may reach 104° F., the febrile movement is not a feature of the disease. The most noticeable symptoms are the frequent stools of fluid feces, mucus, and blood, the pains in the abdomen, and the progressive loss of flesh and strength. The disease may only continue for ten days, or it may be protracted over several months. The same patient may have several attacks of the disease.

A serious complication is the formation of the amœbic abscesses of the liver, which may occur at any time in the course of the colitis, either in mild or severe cases.

Of less frequent occurrence are the amœbic abscesses in the lungs, with cough and bloody, foul-smelling expectoration.

I have seen one case in which the pulmonary symptoms preceded the diarrhœa by three days.

Perforation of the intestine, followed by collapse or by peritonitis, sometimes occurs. There may also be peritonitis without perforation.

I have seen one case which lasted for six weeks with the combined symptoms of a typhoid fever with temperatures up to 105° F. and a colitis. After death there were found the ordinary lesions of typhoid fever in the ileum and the mesenteric glands, and of amœbic colitis in the colon.

The prognosis is serious, not only from the extent of the destruction of the wall of the colon, but from the liability to abscess of the liver, abscess of the lung, and peritonitis.

Treatment. The indications are to use irrigation and drugs. The best irrigation is a solution of corrosive sublimate, 1 to 10,000. The drugs are the same as those which we use in croupous colitis.

6. There is a form of necrotic colitis of which I have only seen a few examples. They were all hospital cases, with imperfect histories and no account of the passages from the bowels. The history of one case will serve as a sample:

A woman, aged about fifty years, of intemperate habits, was brought into the hospital twenty-four hours before her death. It was said that for several months she had been losing flesh. For three days she had been vomiting coffee-ground matter. Nothing was learned concerning the passages from the bowels. She was in a moribund condition when brought into the hospital, with a temperature of 96° F., a pulse of 160, and still vomiting coffee-ground matter.

At the autopsy there were found general bronchitis, small abscesses in the kidneys, cirrhosis of the ilver, a normal stomach and small intestine. The colon for a distance of three feet down from the ileo-cæcal valve was in a condition of intense congestion. There were a number of small and large black thickenings of the glandular coat.

In the glandular coat there were some increase of mucus in the tubules and a little growth of cells between them. In the black thickenings the bloodvessels were distended with blood. The glandular and connective tissue coats were infiltrated with pus-cells. The glandular coat was necrotic. The circumscribed character of these areas of extreme congestion and purulent infiltration would suggest that they were caused by infectious emboli.

There are then five forms of colitis which come under ordinary observation in New York:

1. A colitis without structural changes in the colon, of which the prognosis is good except in children, and which can be successfully treated in a variety of ways.

2. A colitis with purulent infiltration of the connective tissue coat, which is regularly fatal, and for which there is no satisfactory treatment.

3. A colitis with exudation, productive of new tissue and necrosis, the inflammation beginning in the glandular coat, which has a

disposition to continue for a long time, is sometimes fatal, and is difficult to treat satisfactorily.

4. A colitis with exudation, the formation of false membranes, and necrosis, of which the prognosis is serious, and for which the best treatment is the administration of large doses of ipecac and the irrigation of the rectum.

5. A colitis caused by the amœba coli, characterized by necrosis combined with a variety of inflammatory changes, and often associated with similar changes in the liver, of which the prognosis is serious, and for which the best treatment is the administration of large doses of ipecac and the irrigation of the rectum.

As regards the treatment of these different forms of colitis, it seems to me that the first thing to determine is whether the inflammation is confined to the lower end of the colon, or extends higher up. The second thing to determine is whether the inflammation is, or is not, accompanied by necrosis of portions of the wall of the colon.

If the inflammation is confined to the lower end of the colon, it can be treated by irrigation alone. If it is confined to the upper two-thirds of the colon, it can be treated by drugs alone. If it involves the whole length of the colon, both drugs and irrigations are necessary.

An irrigation for an adult should consist of as much as two quarts of fluid, and the fluid must run in and out freely.

If the colitis is acute and without necrosis, the best fluid is an infusion of flaxseed.

If it is a colitis with necrosis, solutions of corrosive sublimate, chloride of zinc, and formalin have given me the best results.

If the inflammation involves the upper part of the colon and is without necrosis, rest in bed, a milk diet, and the preparations of opium and of bismuth are usually all that are necessary. But, if it is a colitis with necrosis, ipecac in large doses, castor-oil in small doses, nitrate of silver, salol, and naphthalin are the most useful drugs.

PANCREATITIS FOLLOWED BY CYST OF THE PANCREAS.

By ALEXANDER McPHEDRAN, M.B.,
OF TORONTO.

Concerning disease of the pancreas there yet remains much to be made clear. Since the publication of the extensive studies of Senn[1] in 1885, and of Fitz[2] in 1889, our knowledge of these diseases has been added to chiefly by the reports of cases, each serving to demonstrate some special characteristics. The following case possesses some features that render it of special interest:

George A. B., aged fifty-three years, a member of the Civil Service. His father had some liver affection, and died suddenly; his mother died of carcinoma of the breast. In all other respects the family history is good.

His own history is good until 1891, when he had his first attack of what appeared to be biliary colic, lasting about one day, with well-marked jaundice and pale fæcal discharges. Otherwise the attack was uneventful and recovery satisfactory. The jaundice disappeared within a few days. After this he had, annually, two or three similar, but milder, attacks. On the first threatenings of an attack he would call upon the nearest physician for a subcutaneous injection of morphine, and then return to his official duties. Each physician of whom he sought relief accepted the diagnosis of gallstone colic and advised operation; one assured him that he had a "gall-bladder full of gallstones." During the winter of 1894–'95 the attacks became more frequent and his health began to suffer, in consequence of which he obtained leave of absence and spent the summer at the seaside. While there the attacks recurred very frequently, but were not severe, nor was there any jaundice. There was indigestion, with considerable flatulence, and almost constantly some degree of discomfort in the epigastrium.

A few days after his return home he was taken with a severe paroxysm of pain, with vomiting and prostration. This was the first occasion on which I saw him since his first attack in 1891. This attack was very severe and not fully relieved until the third day. There were pain and ten-

[1] American Journal of the Medical Sciences, 1885.
[2] The Middleton-Goldsmith Lecture, 1889.

derness in the epigastrium, from which pain radiated in various directions. Vomiting did not recur after the first day; the tongue was heavily coated; no appetite; considerable thirst; bowels constipated. There was slight jaundice and some bile pigment in the urine. The temperature was elevated for five days, rising as high as 101° F. There was fulness in the gall-bladder area, but tenderness was too great to permit of examination of the deeper parts. There was some pain across the back in the lower dorsal region.

He improved gradually, and in ten days—September 16th—he returned to the office. His digestion improved, the bowels being kept open with Carlsbad water, but there was considerable flatulence. The discomfort in the epigastrium persisted, with some tenderness; on deep pressure, slight thickening could be made out about the head of the pancreas and extending to the left. He had occasional attacks of pain, many of them due to intestinal colic. For these he took half a grain of codeine from time to time. In the severe attack he lost flesh, and still continued to fail a little, but he was not emaciated. His complexion was of a peculiar ashy-gray color.

On October 5th it was noted that there was increase in the thickening in the deep part of the epigastrium to the right side; some tenderness. He was feeling ill and had to cease work; but on the 8th, when next examined, a large smooth cyst-like tumor was found in the epigastrium extending from the right parasternal line to the left mammary line and downward to the umbilicus. The upper boundary was ill-defined; stomach resonance was above and to the left. It was most prominent to the left, where the percussion note was flat; there was slight resonance over the right part of it. There was no increase of tenderness. (Fig. 1.) The temperature was 99½° F.; pulse quiet. He was feeling quite ill.

From the sudden formation of the tumor and its situation it seemed evident that it was formed by fluid in the lesser peritoneal cavity, and on account of the absence of symptoms of hemorrhage it was probably a serous accumulation therein. On October 11th, Dr. Irving H. Cameron, assisted by Dr. George A. Peters, opened the cyst by an incision in the median line above the umbilicus and evacuated a large quantity of clear straw-colored serum. The stomach lay in front of the upper part of the cyst, and at the bottom lay the pancreas irregularly enlarged and firm, but somewhat elastic. The peritoneum over it was smooth and healthy looking. There was no sign of hemorrhage anywhere. The liver as far as could be examined was healthy; the gall-bladder could not be reached.

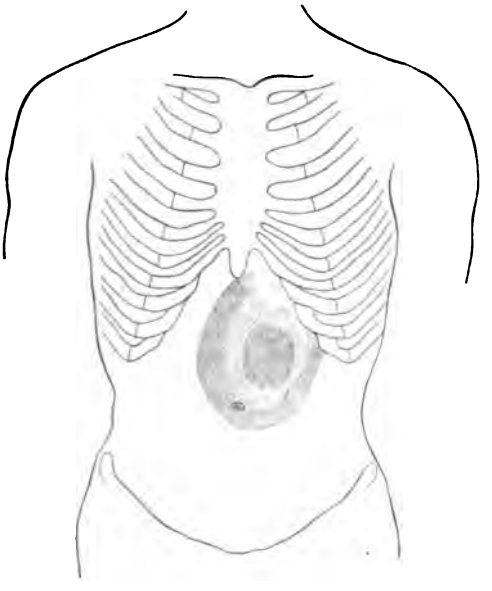
From the conditions found it was thought that probably there was malignant disease of the pancreas, with some inflammation, to which the exudate was due.

The incision was closed without drainage. Next day there was extreme prostration. Pulse 130+, temperature 101½° F.; marked cyanosis and irritable cough, with a little ropy mucous expectoration.

On the following day (13th) he was much better, and continued to do well until the 17th, when the temperature rose to 102°. It fell next day. The

stitches were removed on the 18th; the union appeared healthy. The general condition improved satisfactorily, but the discomfort in the epigastrium required the subcutaneous injection of morphine every night. On the 30th the upper part of the incision opened and discharged half an ounce of thin, white, curdy-looking fluid. It came from a subcutaneous cavity to the right of the incision; there was no pain or tenderness about it, and little evidences of inflammation. It was slow in closing up. It was not an ordinary abscess; unfortunately, an examination was not made of the discharge. It is possible that it was due to an area of fat necrosis. After the removal of the dressings the deep tumor was found to have enlarged considerably.

FIG. 1.

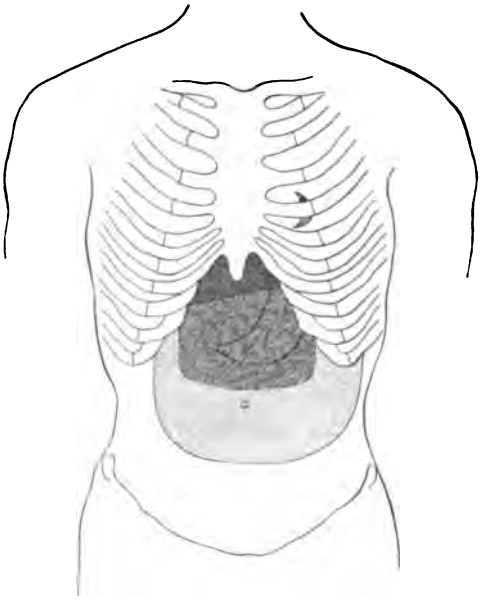


On January 10, 1896, the following note was made: He has improved so much as to be able to resume a moderate amount of his office duty. His face is thin, but has lost the ashy pallor and is of good color. He is flatulent; the tumor is much larger; the stomach lies in front of the upper and left part of it, and is so compressed by it as to give a flat percussion note in the part overlying the tumor. By applying pressure at the left costal margin and extending it to the right, gas can be forced through the pyloric orifice with a gurgling sound. The transverse colon crosses below the tumor. The urine is normal; it has always been free from sugar.

By March 12th the tumor had attained large dimensions, extending downward to the level of the anterior superior spinous process of the ileum and laterally to the mammary line on the right and the anterior axillary line on

the left. It forced the diaphragm upward so that the impulse of the heart was in the fourth intercostal space. (Fig. 2.) Posteriorly it extended into the left lumbar region, rendering it full and upward as high as the ninth rib, producing the signs of effusion into the left pleural cavity. Its anterior surface presented a prominent, quadrilateral area above the umbilicus, over which the percussion note was flat. The tumor felt elastic, but did not fluctuate. There was no pulsation communicated to it by the aorta, nor did it move with respiration.

FIG. 2.



On March 13th, Dr. I. H. Cameron, assisted by Dr. George A. Peters and by Dr. F. R. Eccles, of London, operated. The incision was again made in the middle line in front, and a cyst exposed lying behind the stomach. There were no adhesions. The cyst-wall was about 2 mm. thick. A large quantity of fluid was evacuated. The fluid was opaque, whitish, and contained many flocculi and fibrin masses. Dr. R. R. Bensley, of the University of Toronto, Biological Department, reported that "the fluid contained considerable albumin and held in suspension large numbers of leucocytes of the hyaline polynuclear variety. The solid particles were fibrin flocculi, in the meshes of which were large numbers of the leucocytes. The fluid was slightly alkaline in reaction." This showed the fluid to possess no digestive ferment. On bacteriological examination the fluid proved to be sterile. A good recovery was made, and Mr. B. was able to walk out early in April. The cyst cavity contracted rapidly, but a fistula persisted, extending to the

original depth of the cyst—5¼ inches—backward to upper part of the left kidney. The discharge was free, and in April began to excoriate the surface about the opening. This trouble from excoriation has recurred from time to time since then.

It has been difficult to obtain a sufficient quantity of the discharge to test its digestive power. On one occasion, while Mr. B. was in London, there was a free discharge, which Dr. Eccles examined and found to possess marked action on albuminoids, fats, and starches, leaving no room for doubt as to the presence of pancreatic secretion. Lately, what fluid can be obtained is mixed with slight purulent discharge, so that the pancreatic ferment is rapidly decomposed. It dissolved fibrin, however, but this property may possibly have been due to bacterial products.

The general health is now good. The sinus still persists, the discharge being so great as to necessitate a change of dressing three or four times a day. There is no retraction of the epigastrium, and the probe passes still as far as it did after the cyst contracted into the sinus—5¼ inches.

From the foregoing history it appears probable that the cause of the repeated attacks of colic, during the five years preceding the formation of the cyst, lay in the pancreas. Of the precise nature of the condition giving rise to the disturbance we cannot be certain.

It may have been a calculus or some localized inflammatory process. Such recurrent attacks of pain, protracted over long periods of time, have been ascribed to disease or irritation of the semilunar ganglia and the solar plexus; but the moderation of the attacks on the formation of the cyst, and their complete relief by its evacuation, point strongly in this instance to mechanical obstruction, whether by stone, cicatricial contracture, or external pressure. The attack of September 6, 1895, was probably caused by acute pancreatitis; it was certainly not due to gallstones.

To produce symptoms resembling biliary colic it is not necessary that the obstructing body should be hard and unyielding. Kümmel[1] reports a case with the symptoms of gallstone colic with icterus, in which, at the autopsy, the pancreatic duct was found dilated and containing many rice-grain-like bodies of soft consistence. To these apparently the colic had been due. Körte reports similar experiences. Before the formation of a perceptible tumor some inflammation of the pancreas or the peripancreatic tissue occurred, possibly in repeated attacks, one of which was more severe than the others, and, extending to the omental bursa, caused sudden exudation into

[1] Deutsche med. Wochenschrift, October 29, 1896; Verenos-Beilage, No. 28, p. 190.

it. With the inflammation there seemed to be no hemorrhage ; at least there were no signs of such, either in the serum evacuated at the first operation, or in the appearance of the elongated tumor occupying the situation of the pancreas. Nor yet did the constitutional symptoms present signs of hemorrhage. If this be correct, then the case will occupy another class than any of those given in the admirable monograph by Fitz, in which he divides cases of pancreatitis into the three classes of hemorrhagic, suppurative, and gangrenous. It is quite conceivable that acute inflammation of the pancreas may be produced without the occurrence necessarily of any of these results.

That the cyst was actually formed in the pancreas, there is little room for doubt. The physical characters of the tumor found at the time of the first operation, occupying the situation of the pancreas, could scarcely be produced except by obstruction of the duct of Wirsung. The obstruction probably caused distention of the whole duct and some of its branches, giving rise to the elongated, irregular tumor found at the time.

The character of the contents of the cyst and of the subsequent discharge from the fistula is worthy of remark. That the contents of the cyst contained none of the active elements of pancreatic secretion does not render it even improbable that the cyst was of true pancreatic origin, because these elements may have been present at an earlier period and have become absorbed or destroyed. Nor, on the other hand, does the appearance of pancreatic secretion in the discharge from the fistula at a later date prove that the cyst was developed in the pancreas and not in its neighborhood, for the fistula may communicate with some of the ducts of the pancreas, or the digestive activity of the secretion may be due to the products of bacterial growth. Many instances are recorded in which the contents of cysts in contact with the pancreas possessed both amylolytic and emulsifying properties.[1] Such cysts are probably more frequently found as the result of injury in which the pancreas is lacerated. It is important to note, however, that cystic or other fluid formed in any part of the body may possess considerable emulsifying and amylolytic power, as may also fresh normal urine.[2]

[1] Guy's Hospital Reports, 1892, vol. xlix. p. 286.
[2] Central. f. die med. Wissenschaft, 1897, No. 1.

It is unfortunate that the term pancreatic cyst has been applied, especially of late years, to all varieties of cysts occurring in the neighborhood of the pancreas. Many of these so-called pancreatic cysts result from accumulation of fluid is the omental bursa, or are formed in the transverse meso-colon. This is especially true of the cases following traumatism, and they constitute a large proportion, if not the majority of all cases of cysts reported. On this account it is difficult to make satisfactory analysis of the cases on record, as it is impossible, for want of accuracy in the details given, to separate the cases of pancreatic cyst from collections of fluid in the lesser peritoneal cavity, the transverse meso-colon, and possibly in the adjacent structures.

Attention was drawn to these facts by Jordan Lloyd, in a valuable paper published in 1892,[1] in which he relates two cases of accumulation of fluid in the lesser peritoneal cavity, in one of which the middle two-thirds of a gangrenous pancreas was detached and lay free in the fluid. A similar case to this last one of Lloyd's was reported by W. W. Ashhurst, of Mexico, in 1894,[2] in which a piece of the pancreas lay at the bottom of the cyst cavity, whose contents were sero-purulent. The case is recorded as a cyst of the pancreas. Pancreatic cysts always result from obstruction of the duct, with retention of secretion and subsequent dilatation of the duct; or, in case of a laceration of the gland, from escape of the secretion into its parenchyma and the subsequent dilatation of the capsule into a cyst. Neither of these cases is consistent with such a pathology.

The close resemblance as well as the points of contrast of pancreatic cyst to effusion into the omental bursa are well brought out in the history I have detailed. Both cysts occupied the same area, but differed in shape, the peritoneal effusion extending less to the right and further downward, being somewhat irregular in shape, with its longest diameter nearly vertical, while the pancreatic cyst was somewhat quadrilateral in shape, with the long diameter transversely. The peritoneal effusion took place within a few days, more rapidly than a cyst could form in so firm and friable a structrue as the pancreas; while the pancreatic cyst formed comparatively slowly, increasing steadily in dimension.

[1] British Medical Journal, 1892, ii. p. 1051.
[2] Medical News, 1894, vol. lxiv. p. 377.

The constitutional disturbances attending the development of both kinds of cyst bear a very close resemblance, as indeed they should, because they press upon and injure the same nerve structures, the solar plexus and semilunar ganglia. In the peritoneal effusion, as well as in the pancreatic disease, there may be pain, vomiting, and prostration; emaciation and anæmia may be much more marked than these symptoms would account for. The temperature is usually little disturbed in either affection, and may be subnormal throughout in both. In a case of supposed tubercular disease of the lesser peritoneal cavity closely resembling pancreatic cyst, under observation a few years ago, all these symptoms were very marked.[1] After the cyst was incised and drained recovery was very rapid, the sinus being completely closed in less than a month, with much retraction of the epigastrium. It is probable that herein lies a distinction between the true and false pancreatic cysts, the latter becoming closed in a much shorter time than required by true cysts of the pancreas, especially if some of the gland tissue remains communicating with the cyst-cavity.

Some years ago Senn[2] pointed out that complete obstruction of the pancreatic duct uncomplicated by morbid changes in the parenchyma of the gland never resulted in the formation of a cyst, the pancreatic juice accumulating in the duct being removed by absorption. If, however, pathological changes have occurred in the gland, absorption of the fluid is interfered with and gradual distention follows, it may be, to enormous proportions. In this case repeated attacks of inflammation of the organ probably took place, the most severe being in September, 1895, and a second one before the sudden distention of the omental bursa with serum.

It has been thought that true, as well as false, pancreatic cysts are due to hemorrhage, and that the hemorrhage results from a lesion of the sympathetic system.[3] The first proposition is doubtless generally true of cysts following traumatism, but of those originating apart from traumatic causes, in many—perhaps the majority—no hemorrhage takes place. In the case here detailed is an instance of a true pancreatic cyst without hemorrhage.

[1] Canadian Practitioner, 1892.
[2] American Journal of the Medical Sciences, 1887, vol. xciii. p. 135.
[3] Fisher: Guy's Hospital Reports, 1892.

There is ample evidence in this case in the preservation of a good state of nutrition and general vigor, together with the absence of excess of fats and of undigested proteids in the fæcal discharges, and of any symptoms of diabetes, that a part of the gland remains intact, discharging its secretion into the intestinal canal as well as furnishing to the blood the "internal secretion" peculiar to it, without which general metabolism would be deranged. At no time during his protracted illness did he apparently suffer from derangement of the function of the pancreas.

ANGINA PECTORIS: ITS RELATION TO DILATATION OF THE HEART.

By J. H. MUSSER, M.D.,
OF PHILADELPHIA.

THE purport of the following paper is the consideration of angina pectoris, insomuch as it bears relationship to dilatation of the heart. It includes an estimate of the influence of this relationship in the prognosis and treatment of the subjective symptoms (pain) on the one hand, and of the organic condition (dilatation) on the other. The paper is entirely clinical, and is a record of the writer's observations, not of angina pectoris, but of such of his cases of this affection which manifestly exhibited the relationship above mentioned.

It will be appreciated, the writer trusts, that he is fully cognizant of the difficulties that attend a diagnosis of *angina pectoris;* that he is alive to the fact that, in spite of consummate care, we may err in the diagnosis; that he is aware that the occurrence of cardiac pain is not alone sufficient to admit of the diagnosis.

The presence of the symptom-complex, so skilfully portrayed by the earliest historians of this affection, Heberden and Jenner, and more fully elaborated by Latham and Gardiner, is essential to the formation of a diagnosis, although we cannot fail to agree with the dictum of the latest author, our distinguished colleague, Professor Osler, that "pain about the heart of an agonizing character, occurring in paroxysms, is the dominant feature."

We will all admit, also, that in angina pectoris we are confronted with the facts that it usually occurs in males, that it is an affection of the latter decade of life, that the patients are of the better class, usually well fed, and that they are often the victims of other affections (gout, diabetes, etc.), indicating a more or less sedentary life with an abundance of food, which contributed to the physiological hypertrophy that proceeds with advancing years.

Before proceeding further it may be well to state that we can reasonably infer the presence of dilatation of the heart by the physical signs of displaced apex-beat, gallop-rhythm, a soft regurgitant murmur in the tricupsid or mitral area, by venous phenomena, and by the congestions, cyanosis, and dropsy that attend this affection. The results of cardiac percussion may be confirmatory, but are not looked upon as essential in the diagnosis of cardiac dilatation.

Bearing in mind these fundamental propositions, the writer begs to submit cases (it is to be regretted they are too few) to illustrate the following point:

1. When dilatation of the heart supervenes in a patient the subject of an attack or attacks of angina pectoris, the subjective symptoms may subside. At the same time the physical type of the individual changes.

2. Angina pectoris may occur in a patient who has had dilatation of the heart, after the organic condition (dilatation) is removed by treatment.

3. True angina, when it occurs in dilatation of the heart, admits of a prognosis more favorable than when it occurs with other mural conditions, as myocarditis, etc., without dilatation.

4. Grave cases of dilatation of the heart, conversely to the above, may be looked upon as amenable to successful treatment if the patient should have paroxysms of true angina pectoris.

5. In the treatment of angina pectoris digitalis is of doubtful value, not to be given unless there is an excess of dilatation.

6. The pain of angina appears to be due to increased contra-ventricular pressure, although other causes are no doubt operative.

CASE I. *When dilatation of the heart supervenes in a patient the subject of an attack or attacks of angina pectoris, the subjective symptoms may subside.*— A. W. R., aged sixty-seven years, merchant, consulted me for dyspnœa and pain, April 3, 1894. Smoked to excess, but did not use alcohol. He had been subjected to severe mental strain. He took but little physical exercise. He had inflammatory rheumatism in 1874; otherwise previous health good.

The patient observed the first pronounced dyspnœa and severe pain after ascending a steep incline. He had had moderate dyspnœa and oppression on exertion previously; but the attack just referred to was such as to compel him to discontinue his efforts. It was noticeable, too, because it was attended by a cold perspiration, and the patient was compelled to assume a fixed position. The attack was followed by others in rapid succession. Subse-

quent attacks in April and May were attended by pain down the left arm as well as in the præcordia.

Physical Signs. On the occasion of his first visit it was noted: apex not visible, impulse weak, area of dulness not increased. There was an impure systolic sound at the apex, not transmitted; a short, high pitched tricupsid valve sound; a loud accentuated second aortic, very pronounced at apex and xiphoid. The pulmonic second could scarcely be distinguished. The temporal arteries were prominent. The radial showed very high tension. There was an arcus senilis. There was a trace of albumin and a few hyaline casts. The condition of the other organs was not of material value. Diagnosis: myocarditis, faintly incompetent mitral valves. Endarteritis.

The patient remained under observation until his death, thirteen months after the original attack of angina. This time may be divided into two periods: the first was of about three months' duration. During April, May, and June of 1894 he suffered from frequent attacks of angina, but lessening in frequency and violence each week. Notwithstanding the relief he experienced he lost flesh and strength, and was confined to his bed. At the same time cardiac symptoms of dilatation ensued. His dyspnœa increased, cyanosis became more marked, and œdema developed. The most striking feature was the change in the type of the man. In April he was hale, with ruddy face, strong voice, and vigorous walk. In July he was pallid, with pinched features and sallow complexion. His form was stooped, his voice feeble. He was very weak, and only by the greatest care he was moved to the seashore.

During this time the area of cardiac dulness increased; it extended each week until the left border was two inches beyond the original limit. The right heart enlarged. The second sound lessened in intensity at the aortic; increased at the pulmonary orifice. The localized mitral impure sound became a loud mitral systolic murmur, transmitted into the axilla. The tension of the pulse lessened and it increased in frequency.

At the seashore he gained flesh and strength—particularly the latter—but never was the same. During the winter the picture changed. Pain was a minimum symptom; chest oppression was present, dyspnœa was extreme; insomnia; moderate cyanosis and œdema were present. The dyspnœa and weakness were the principal symptoms. He had dilatation of the heart and mitral insufficiency.

The fall and winter months were occupied by the second period of the disease. Dyspnœa continued to be the most serious symptom. The dilated heart grew in size and lessened in strength. An aortic regurgitant murmur developed. Pain was not complained of, and, although he had alarming attacks of dyspnœa, he never had an attack of angina. Notwithstanding the dyspnœa the patient went about the house, and daily, weather permitting, took short walks, always careful to eschew elevations.

In April, 1895, he had severe attacks of cardiac asthma, and May 6th he had a most pronounced and typical attack of angina pectoris *sine dolore*, resulting in death in about twenty minutes.

The case was interesting because of the vivid portrayal of the change of the physical type of the individual; because of frequent attacks of angina pectoris during a period of comparative cardiac hypertrophy, when increased intraventricular pressure could not be relieved; because of the relief to pain obtained by the onset of dilatation, and because of death from angina without pain when intraventricular pressure was lessened.

CASE II. *Angina pectoris: rapid cardiac dilatation with relief of pain; death from dilatation.*—M. B. M., aged forty-one years, male; physician. The patient was moderate in the use of alcohol and tobacco, but enjoyed and indulged in good, rich food. He was subject to rheumatism, and had in early life one attack of rheumatic fever with pericarditis. The family history was that of rheumatism and gout. The patient was robust, plethoric, and overweight, although not unduly. He was an excellent specimen of physical manhood. After exertion, early in January, 1888, he was seized with an attack of angina pectoris. In twenty-four hours he had an attack of active pulmonary congestion. The congestion was attended by acute cardiac dilatation with a mitral murmur. Angina never recurred. He improved, but never could leave his room, and in February the dilatation became more pronounced. He died in March from the consecutive congestions due to the dilatation. The autopsy showed atheroma of the coronary arteries, thrombosis, myocarditis, aneurism at the apex of the left ventricle, great dilatation of all the cavities.

It is of interest to note that after the first twenty-four hours cardiac pain disappeared with the onset of dilatation. The rapid onset of the pulmonary congestion was induced by mitral incompetency, which also relieved apparently the pressure within the heart, and in consequence the pain.[1] It is possible the pain was due to the plugging of the coronary artery, as we know occurs when a peripheral vessel, as the brachial, the popliteal, etc., becomes obstructed by embolus or thrombus. The symptom-complex of angina pectoris was so marked, however, that the nature of the affection could not have been mistaken.

CASE III. *Angina pectoris; dilatation; relief; death from remote effects.*—Mrs. L. consulted me in 1890. She was then sixty years old, robust and energetic. At that time she had frequent attacks of biliary colic. She never had rheumatism. In 1891 she had a mitral systolic murmur and suffered from dyspnœa. She took digitalis over a considerable period of the year. In 1893 the records are found of aortic obstruction and mitral regurgitation. She began to suffer from angina pectoris, and in 1893 and part of 1894 had

[1] See Balfour, The Senile Heart, 1894, p. 136. A similar case is related.

many severe typical attacks. The heart was hypertrophied. She suffered from vertigo and headache. In 1895 Mrs. L. lost flesh and strength and became anæmic. She also had albuminuria. No attacks of angina occurred from October, 1894, to 1897. During this time the heart became dilated, and she suffered from the symptoms thereof. Curiously, only in 1895 and 1896 were the signs of mitral obstruction present (see autopsy). In January, 1897, death took place from cerebral thrombosis.

The *autopsy* performed by Dr. Steele was as follows:

An elderly woman; subcutaneous fat well preserved; some cyanosis, but no œdema; both pleural sacs are about half full of clear, straw-colored fluid. The lungs appear healthy; the pericardium is normal, and does not contain fluid. The right auricle is enormously dilated, and projects well to the right of the sternum; the left auricle is also greatly dilated, but not to the extent that the right is. The heart is much enlarged, and the apex extends to the left of the mid-axillary line. The left ventricle contains some soft clots; it measures 20 mm. in thickness and 10 cm. in length. The myocardium is pale and friable; the papillary muscles show an exquisite mottling of yellow areas, the intermediate spaces being of a dark red. They appear almost cystic, and are so degenerated that they cannot stand upright by themselves.

The muscle of the ventricular wall shows numerous scars throughout its substance.

The leaflets of the mitral valve are thickened by extensive fibrous change; the edges of the leaflets are somewhat adherent; the chordæ are thickened and shortened; the valves admit two fingers to the first joint; the aorta above the valves shows considerable atheromatous change; the valves themselves, though slightly thickened, appear to be competent. The right ventricle is dilated; its walls measure 6 mm. in thickness. The tricuspid valves are normal but dilated, and admit five fingers to the second joint.

The weight of the heart is 480 grammes. The coronary arteries are exceedingly atheromatous and rigid, particularly in the upper portion; they do not contain thrombi, but are filled with marantic clot; the deposit of fat around them is somewhat excessive. The arteries throughout the body show a considerable degree of atheroma.

The kidneys are small; the capsule strips badly; there are numerous cysts on the surface of the cortex, which is irregular and scarred; the cortex is contracted, and the consistency of the organs is increased.

The liver extends below the costal margin in the mid-clavicular line.

The gall-bladder is small, thickened, and opaque; the upper third is separated from the rest of the sac by a cicatricial contraction giving the sac an hour-glass appearance; the small portion is completely filled with soft yellow gallstones; the lower portion contains a few small loose ones.

The stomach was small and measured but six inches from the cardiac orifice to the pylorus. Its wall was thickened.

While under observation the patient became a frail and feeble woman. Her physical type changed, as we saw in Case I. During

the period of relatively good health and robustness she suffered from angina; in later years the pain entirely disappeared.

CASE IV. *Angina pectoris; dilatation; restored hypertrophy; return of angina.* —Miss G., aged sixty-eight years when attended by me in 1892 on account of typical attacks of angina pectoris. She had had a severe attack of rheumatism previously, and in 1890 an attack of protracted influenza. Her health failed to an extreme degree after the attacks of angina. There were aortic obstruction and mitral regurgitation, and rapidly following the angina, dilatation of the heart supervened. During part of 1894 and all of 1895 she was unable to leave her room, and required the attendance of a maid on account of cardiac debility. She did not have angina. She took digitalis. In 1896 she grew stronger and went about the house. The heart regained force, and compensatory hypertrophy seemed to be established.

In November, 1896, attacks of præcordial pain recurred and one attack of true angina. Death took place suddenly. Physical examination two weeks before death showed that the heart had regained vigor and was the seat of dilated hypertrophy, as the following signs indicate. There were no evidences of dilatation in excess.

Apex-impulse in fifth interspace, in mid-clavicular line plainly visible and somewhat diffuse. Cardiac dulness right border, right parasternal line; upper border, lower border third rib; left border 2 cm. left of mid-clavicular line. No pulsation in vessels of neck and very slight in epigastrium. No thrills. Apex first sound (mitral), soft systolic murmur transmitted to axilla.

Aortic. With first sound harsh, blowing murmur transmitted to vessels of neck and toward apex. Second sound accentuated.

Tricuspid. First sound a soft, blowing murmur entirely different in quality from the other areas, transmitted up and to right about 3 cm.; second sound clear. *Pulmonary*, first and second clear and pure.

Autopsy. Heart. Pericardium is normal. The heart is much enlarged. The right auricle is much dilated and extends to the præsternal line in the right.

The myocardium of both ventricles is hypertrophied and both are dilated, the right especially.

The left ventricle measures 20 mm. in width. The right 8 mm. Weight of heart 480 grm. There are many scars throughout the myocardium of the left ventricle not localized to any one locality. The mitral valve is contracted, evidently by old inflammatory processes, and barely admits the first joint of the first finger. The tricuspid orifice is dilated and admits three fingers easily, and four to the second joint. The valves are slightly thickened along their free edge, but there is no evidence of acute inflammatory change.

The conus arteriosus of the aorta is contracted, evidently from a congenital malformation, and at its narrowest point (just below the valves) measures 15 mm. in diameter. The aortic valves are exceedingly thick and studded with calcareous nodules, but appear to be competent. The aorta is very much

thickened, and there are calcareous plates about each coronary artery. The coronaries are thickened and calcareous throughout almost their entire extent. Dissection shows no thrombosis or embolism.

It was remarked in the careful notes of the *autopsy*, taken by Dr. Steele, that there was no evidence of passive congestion of the internal organs the result of cardiac dilatation.

The case presented during life an early period of aortic and mitral stenosis, with hypertrophy, during which attacks of angina occurred; a middle period of failing compensation without angina; and a final period of restored hypertrophy and angina.

CASE V. *Angina pectoris following the relief of cardiac dilatation.*—Mr. P. G. was attended by me three years ago during an attack of pneumonia. He was then seventy-five years old. He had been an active, prosperous merchant, but had withdrawn from business five years before. He was temperate in all things. After the pneumonia there was prostration, and dilatation of the heart supervened. For six months he was short of breath, the heart was irregular and intermittent, and a gallop rhythm and systolic mitral murmur were heard. Subjective signs disappeared soon, and last year the murmur could not be heard. Indeed, he rode a bicycle for a time. In January, 1897, he had an attack of influenza. The heart became irregular and intermittent, and he had oppression and dyspnœa. There were no signs of dilatation. There was high arterial tension. Digitalis was given with nitroglycerin during January and February, because of the old dilatation. Two months ago he began to suffer from angina pectoris. The attacks have persisted, although less frequent since digitalis was discontinued and large doses of nitroglycerin given, which drug also controls the pain.

Physical examination shows strong impulse, no venous phenomena; no thrills; no murmur; occasional gallop rhythm in the anginal attacks; pure and strong first sounds. Pulse shows high arterial tension. No objective evidence of dilatation.

The patient undoubtedly had: first, dilatation of the heart; second, complete recovery; third, angina pectoris, the pain being paramount because of firm muscles. Digitalis was given with nitroglycerin at first because of the old history of dilatation. It was taken in a greater amount than required, on the patient's responsibility, and the writer believes it influenced the onset of paroxysms. The angina continued, but was not relieved in severity or frequency of attack until the digitalis was discontinued.

CASE VI. *Dilatation of the heart; angina pectoris when the dilatation was at its height; recovery from both.*—A. S. G., aged sixty-three years, consulted me

in the summer of 1895 for swollen legs and dyspnœa. He had a systolic mitral murmur. He grew worse in spite of treatment, and was ill the entire winter of 1895–'96 and the summer of that year. He had general anasarca, ascites, and hydrothorax. His chest was tapped frequently. During the spring of 1896 he had frequent attacks of angina pectoris. He has recovered entirely, although physically a different type of man than formerly. Of course, the valvulitis remains. Digitalis could not be given. Strophanthus and nitroglycerin were the only drugs he could take, and these were only admissible at times. Time forbids discussing the treatment or management of the case, in which I was ably assisted by Dr. Scott.

The conclusions from the study of this case were that when angina pectoris occurred in the course of valvulitis and dilatation, it was not necessarily fatal; moreover, its very occurrence showed there was a strong resisting ventricular wall, and that we could therefore hope for a restoration of the heart-muscle.

From the above studies it seems we are warranted in the belief that the pain of angina pectoris is often due to increased intraventricular tension; and that the subsidence of pain when dilatation of the heart comes on occurs because of incompetency of the valves permitting of relief to the pressure. By this means may we not explain the infrequency of angina in mitral regurgitation, and similarly its infrequency in females and in young subjects in whom muscles of the heart are not as firm and unyielding as in males? It is well known with advancing age the heart hypertrophies. Similarly might we not infer that the inmates of hospitals and the poor are free from angina because the heart-muscle in this class are not as firm or as completely hypertrophied. It is interesting to observe that the cases of angina *sine dolore* (as Case I.) are the subjects of dilatation of the heart.

In conversation with my friend, Dr. Charles Reed, on this subject, he called my attention to the reasonable analogy that might be traced between glaucoma and angina, and especially to the parallelism of the physical features of the eye and the heart, in both of which increased tension within is attended with pain. The notes of Dr. Reed are of interest and well worth including:

Normal intraocular pressure may cause bulging of the globe (1) when its walls have been weakened by disease (bulbar ectasis from intrauterine choroiditis, staphyloma posticum scarpæ), or (2) are abnormally thin (keratoconus, posterior scleral protuberance of Ammon). Increased intraocular tension under similar conditions is naturally still more apt to be followed by

ectasis. The entire eyeball may become enlarged in all its dimensions if increase of tension occur in infancy or early childhood, when the ocular walls present a certain degree of elasticity (hydrophthalmos).

Later in life the eyeball loses its elasticity and becomes hard, rigid, and unyielding, and increase of tension can produce no enlargement. It does, however, give rise to ectasis at one point—*i. e.*, where the sclerotic is weakened by the separation of its fibres to admit the passage of the fasciculi of the optic nerve. This less resistant part of the sclerotic, the lamina cribrosa, as it is called, gives way before the increased pressure from within, the head of the optic nerve is forced back into the concavity thus formed, and finally atrophies in consequence of the pressure to which it is exposed, the inner surface of the globe presenting a depression at this point.

Increased intraocular tension is the immediate cause of the disease known as glaucoma. The especial form assumed by this affection, and the difference in the symptomatology of the different varieties of the disease, being due to variations in the degree of tension, in the rapidity of its development, and in the amount of resistance offered by the ocular walls.

If the increase of tension be gradual and the coats of the eye elastic, the organ may, as in hydrophthalmos, attain enormous proportions with no subjective symptom other than gradual failure of vision.

Even after the walls of the eye have become rigid the glaumatous process may run its course and destroy vision painlessly, if the tension has not been greatly increased, and has been gradual in its development (glaucoma simplex).

This symptom-pain is due to relative or absolute rigidity of the globe. Although the coats of the eye may still possess some elasticity, they are, nevertheless, relatively rigid if they cannot adapt themselves to increase of intraocular tension.

Except in the first years of life the ocular tunics are, notwithstanding their flexibility, inelastic, and their rigidity increases with advancing age, particularly if arterio-sclerosis be present.

Glaucoma inflammatorium, the type of acute primary glaucoma, occurs most frequently between the ages of fifty and seventy, a period at which the physiological rigidity of the ocular walls is apt to be still further increased by the atheromatous change so often met with at this time of life. Under such circumstances marked reaction follows increase of intraocular pressure. The most prominent subjective symptom is pain. It is very severe, and neuralgic in character. It is not confined to the eye, as in angina pectoris, but radiates from it along the first and second branches of the fifth pair. The patient complains of headache and agonizing pain, now in his eye, now in his ear, and again in his teeth, and his anguish is such that he can neither eat nor sleep. Vomiting is sometimes present, and there may also be fever. The objective symptoms are those of violent inflammation. The conjunctiva is chemotic and injected; there is œdema of the lids, etc.

Anything that tends to produce congestion of the eye, especially venous congestion, may cause an attack. Over-exertion, immoderate eating, nervous

excitement, as from rage or anxiety, are often sufficient to precipitate an attack. Measures that diminish the tension relieve the pain.

PROGNOSIS. A word further of the prognosis in angina pectoris. I. The onset of symptoms and signs of dilatation in angina pectoris render it safe to predict the highly probable relief to the anginal symptoms. II. At the same time we can also predict that the type of the individual will change, and that the onset of the cardiac condition is the beginning of senility; that henceforth business cares, etc., must be set aside and that a life of ease must be led, if the years of life are to be added to. III. Angina pectoris in the course of dilatation of the heart admits two favorable elements in the prognosis: *a*, death will not take place from angina in the large number of cases; *b*, the dilatation will in most cases be restored.

DISCUSSION.

DR. WHARTON SINKLER: The question as to the cause of pain in angina is one of great interest, and it seems to me that it cannot be due to intraventricular pressure alone, but that there are other conditions in the arterial system which produce it. In pseudo-angina the pain is just as great as in the organic form of the disease. I recall the case of a hysterical girl who had attacks of angina which were intensely painful; in fact, as severe as any case of true angina I have ever seen. The pain was so violent that hypodermatic injections of one grain of morphine failed to relieve her. She was removed from the influence of sympathizing friends, and with appropriate treatment was speedily relieved of pain. I believe there must be some other explanation of the pain in angina than that given by Dr. Musser.

DR. H. C. WOOD: I have listened with a great deal of interest to the very suggestive paper read by Dr. Musser. If the pain of angina pectoris be caused by an increased intraventricular pressure, the natural inquiry is, what causes this excessive intraventricular pressure? It can scarcely come from a condition of the heart itself, so much as from a state of the blood-vessels. If the blood-pathways be wide open, moderate cardiac hypertrophy does not necessarily greatly increase the intraventricular pressure. If, however, the blood-paths be in part occluded, the intraventricular pressure must be great, even if the heart be not hypertrophied. If, therefore, the pain of angina pectoris were really the outcome of increased ventricular pressure, general arterial conditions should play at least as important a rôle as the states of the heart in its production.

The relief produced by the amyl nitrite in angina is certainly accordant with the theory advanced by Dr. Musser, since its first effect is to widen out the blood-paths, and probably greatly reduce the resistance to the ventricular contraction. If the resistance theory be correct, angina pectoris should be immediately relieved by a large hypodermatic injection of aconite, which would certainly rapidly do away with increased ventricular pressure; I doubt whether many of us would like to use this remedy. Digitalis has sometimes, in my hands, seemed, given hypodermatically, to do good in angina pectoris. According to the theory under discussion, it should vastly augment the pain. After all, angina seems to me to be nothing but a symptom, and probably is of varying pathology. Certainly at present we cannot, according to my thought, connect different forms of heart-pain with different lesions.

In connection with the present matter it is interesting to note that in certain cases of insufficiency of the mitral valve, with failing heart, digitalis, instead of bringing relief, increases greatly the cardiac distress. According to the theory which I have long taught, this is due to the fact that the increased ventricular systole produced by the digitalis drives so much blood back through the widely patent mitral orifice as to increase the intraventricular pressure above the point that can be withstood by the thin, softened walls of the auricle. It is possible that one source of heart-pain may be similar to that just spoken of in its production; certain portions of the heart-muscle being so weakened that any increase in the intraventricular pressure may cause them to stretch and give way; but I do not believe that these cases represent true angina pectoris, if, indeed, there be such a thing as a true, distinct angina pectoris.

DR. E. G. JANEWAY: In relation to the theory of Dr. Musser, I will mention certain cases which do not seem to support it. The first relates to a gentleman of sixty-eight years of age, who had been free from any marked evidence of cardiac disturbance. An elevated car, preceding the one which he occupied, ran off the track while he was returning home about six o'clock. At eleven o'clock that evening he was seized with severe precordial anginal pain, which ran into his right arm. At the same time he became of an ashy gray color, but under stimulation and the recumbent posture he rallied. I did not see him until the third day, when pericarditis developed. More or less pain continued in the precordial region and in the right arm. Later, a slight pleural effusion on the right side also developed. The question of diagnosis in this case, at the time I saw him, was not an easy one. The severe anginal attack at the outset, followed two days later by pericarditis, had to be explained, and I ventured the diagnosis that a thrombosis of the coronary artery and a possible partial rupture of the heart were the most tenable hypotheses. The patient lived a week, and on one occasion, contrary to orders, walked to the water-closet. He died as the result of sudden exertion while partially delirious; intending to jump over the foot of the bed, he fell back dead. The autopsy showed a thrombosis completely obstructing the right coronary artery, which, with the left, was the seat of advanced cal-

careous degeneration. The septum of the left ventricle was torn from just below the aortic valves almost to the apex, and down to the endocardium of the right ventricle. A thrombus filled the rent. One of the papillary muscles of the mitral valve was also torn.

A second illustration is that of a gentleman who had died suddenly, being alone in the house with his housekeeper. It seems that three weeks before his death, while crossing a field, he had had a severe anginal attack. His death was considered somewhat suspicious, as all that could be learned was of sudden death at a late hour in the evening, and the previous attack was only learned of after the post-mortem examination had been made. The autopsy was made at night in the country by lamplight, and at first it seemed as if no satisfactory cause existed. I re-examined the heart, which had appeared normal, and on dissecting and opening the coronary arteries found one completely obstructed by a thrombus, and the other two-thirds filled in a similar way. The left, which was completely obstructed, had an older thrombus than the right.

Two other cases are also of interest. In one there existed a gummous infiltration around the aorta just above the heart, narrowing the coronary arteries, and in another there was an endarteritis of the aorta, with patches involving the point of emergence of the coronary arteries so that a small pin could hardly enter.

Again, we may meet, as the following, cases in which the arterial tension is low, which agencies such as nitroglycerine, nitrite of amyl, and iodide of potassium do not relieve. Such an instance came under my observation in a gentleman who had had attacks for years and finally died in one. No autopsy was obtainable. It seems that such cases do not support the theory. Of course, we all meet people with arterial sclerosis and high-tension pulse who, on excitation, have severe precordial distress and anginal attacks. These are, it seems to me, to be explained by heart-strain against resistance in the arterial distribution.

DR. CHARLES CARY: I would like to question one other statement made by Dr. Musser concerning the true lesion of glaucoma. That there is increased intraocular tension is certain, but the tension is only a symptom, as is also the blindness, the true lesion is the alteration of the vessels which will allow of the increased secretion and the production of over-tension. The same can be said of angina, that intraventricular tension is the cause of the pain in some cases may be true, but it is also true that other influences give rise to the anginal symptoms, and when you relieve ventricular tension you do not always relieve the angina.

DR. J. H. MUSSER, in closing the discussion, said: I simply wished to lay stress upon the fact that when there is dilatation of the heart, with safety-valve action, the pain of angina is relieved. In those cases, on the contrary, where there is hypertrophy of the heart the pain continues, and we usually see angina pectoris in individuals who are relatively strong and robust and

possess a strong heart. There has been no attempt to explain all the causes of angina pectoris, because we do not yet understand what it is or its many causes. I have simply tried to show the relation between angina pectoris and dilatation of the heart.

DR. FRANCIS KINNICUTT: The cause of anginal pain in angina pectoris is an interesting question. Increased intraventricular pressure may be regarded as a probable factor in many cases, but it fails to explain the pain in cases of the kind described by Dr. Janeway. It has been suggested that the pain is a *vessel* pain, the result of thrombosis or angeiospasm. The exquisite pain usually present in the blocking of a great systemic vessel by a thrombus or embolus is generally recognized, and probably proceeds from the injury to the sensory nerve filaments distributed to the arterial walls.

DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS WITH RESPECT TO CERTAIN DISEASES OF THE UPPER AIR-TRACT.

By BEVERLEY ROBINSON, M.D.,
OF NEW YORK.

I FEEL quite sure that none of those who are present would be inclined to question the great advances which have been made during the past twenty years or more in the diagnosis and treatment of many affections of the upper air-tract. Thanks to the use of the laryngoscope and rhinoscope, we have before our eyes the diseased appearances of the throat and nose. Taken with the functional disturbances which accompany them in greater or less degree, and with microscopical investigation, frequently of diseased tissues which may be and are properly removed at times by surgical means, a very accurate statement can be made of the intimate nature of the pathological lesion. Whenever, for sufficient reason, pathological examination cannot be made during life, as, for example, when no operative procedure has been instituted, and if death occurs later, investigation enables us to define closely the diseased process.

While the foregoing will doubtless be admitted, the other side is surely true, viz., that with the greater insight into certain conditions which at first appear to be local in their origin and march, the constitutional influence is apt to be ignored in a measure, and the symptoms in the main are accounted for too much by mere local changes. Thus it has become true that local applications, operations, various, simple, or difficult, are believed to ameliorate or cure, and the general system is comparatively little if at all considered or attended to. It has seemed to me that the later German school of medicine is responsible largely for this somewhat narrow and unfortunate interpretation of diseases of the upper respiratory tract.

General appreciations of disease—general pathology—the philosophical combining of many local expressions of impaired function under one head—that has been in my judgment the work of the French school. With them it is not new. It goes back far. It began, indeed, with Broussais, was carried on by Bouillaud, Trousseau, Grisolle, and those of our own day and time, and still remains. There is *juste milieu*, or happy medium, and this is the true goal of the diligent worker, the careful observer, the searcher after truth.

Ten or fifteen years ago every well-educated physician who had given even limited attention to the study of nasal or throat affections provided himself with a suitable atomizing apparatus, and was convinced that by frequent applications of a spray, astringent or soothing in nature, he could allay effectually many inflammatory affections. Even at that time internal medication of the upper respiratory tract was considered to be of secondary importance by very many men skilled and learned in their art. By and by they found that these inflammatory conditions were not always relieved or cured after this manner, and they quickly sought the solution of the problem. In the nose it was affirmed hypertrophy of the turbinates, or a deviated septum, existed, and these were the underlying pathological conditions which occasioned repeated acute inflammation locally.

When this opinion was firmly established we know how soon the period came when frequent operations on the offending structures were performed. The turbinates were cauterized, chiselled, trephined, excised. Numerous ingenious devices rapidly accumulated for straightening the septum, for excision of redundant tissue, for planing down all bulgings or irregularities. Despite all this doing, and the rapid increase of the specialists in diseases of the throat and nose, it was found that nasal and throat affections were none the less prevalent. To-day I am happy to say there is a manifest tendency on the part of a few to acknowledge the governing forces in the economy. These physicians recognize at present that a septum is often irregular and deviated among perfectly healthy individuals; they know that the better way of keeping down a growing hypertrophy of the soft tissues over the turbinates is to give mild aperients to act on the liver, to treat with appropriate, general means every acute coryza which develops, and not let it run its

course unchecked. They know that the gouty, rheumatic, lithæmic, malarial, syphilitic dyscrasia will excite and produce inflammatory action of the pituitary membrane despite the more careful hygiene, unless wise indications of treatment are carried out carefully and intelligently. Nor is this all. They know that fatigue, bad air, damp, changeable atmospheric conditions, will also promote these manifestations; and yet they also recognize that there are times when a conservative local treatment, or well-considered operation, is the only satisfactory method of securing good results.

Again, some of my *confrères*—the specialists—know at present that when a surgical procedure is adopted, and in order to be successful, attention should be paid to surgical methods; and by this I do not mean merely to understand what operation should be done, and to have the skill and courage to perform it; but they must also have the means and opportunity and knowledge to treat the patient's nose with aseptic precautions before, during, and after the operation. In this way, and this way alone, are many operations justified by the ultimate benefit which the patient receives It behooves the general practitioner to recognize when and where he can acquit himself properly and conscientiously. In order to know this much it is not essential to be a specialist of nasal and throat affections. It is necessary, however, to acquire moderate skill in the use of the rhinoscope and laryngoscope, and afterward to make use personally of the correct treatment or pass the case over for awhile, at least, to one who has sufficient knowledge and conscience to treat it properly.

Take, for example, a very large number of persons who have a so-called nasal catarrh. They may be adults or children, marked by obstruction of the nasal passages, and carried to that degree, very often, that they become more or less habitual mouth-breathers. Some there are in whom the mouth-breathing only occurs at times, and during or subsequent to an attack of coryza; others there are who for many weeks or months, and especially at night, in the recumbent posture, cannot get air enough through the nasal passages. Very many cases of both types can be completely relieved by one or more mild cauterizations with monochlor or glacial acetic acid. These acids are rapidly and efficiently applied to the nasal mucous membrane by means of a flattened probe wrapped with cotton. A 2 per cent. solution of cocaine is sprayed into the nasal

passages a few moments previous to the application of the acid, and all pain of it is abolished. The nares are covered with a little vaseline in advance, and all risk of irritating the skin is avoided. An antiseptic spray through the nasal passages after the cauterization, and the use of a borated cotton plug in the nares for a few hours, take away the bare possibility of any subsequent complication. In a few days the patient blows into his handkerchief a few shreds of mucous membrane, white in color, and great if not absolute relief of breathing quickly follows.

Another example of a very frequent ailment in adults and children, with or without nasal obstruction, is the frequent dropping of mucus or muco-pus from the nasopharynx into the throat. It occasions cough, bad breath, disordered digestion. To men and women it is a source of extreme annoyance, and even disgust, from the fact that they are frequently compelled either to swallow this offensive, nauseous secretion or to expel it by efforts of hawking and expectoration. Children are awakened at night with choking attacks, laryngismus, night-terrors, obstructed breathing, thus occasioned. How can it be relieved? By general medication alone? By change of air? By dieting? Very rarely, if ever. Will inhalations or atomized solutions through the nose relieve the condition and obviate the subsequent phenomena? Frequently they ameliorate for awhile; very exceptionally they do more. In adults direct astringent or antiseptic applications to the nasopharynx of tr. ferri perchlor. and glycerine, tr. iodinii co., of carbolic acid and glycerine, will often be of great service in a very short time. To still further augment their value, however, we must often attend to general conditions, and here, again, anæmia, impaired nutrition of different causation, the herpetic diathesis, must be taken into account and wisely treated. For many such a sojourn at an alkaline or sulphur spa abroad—in France or Germany—will help us wonderfully to attain a lasting cure.

In children we should constantly bear in mind that such symptoms, if persistent, will often indicate a more or less considerable development of adenoid tissue. Here, again, the local applications before mentioned may prove to be very useful; but if the mass of tissue be at all pronounced, and the child be in relatively poor, general health, they are insufficient. To secure absolute relief we must

depend on direct removal of the tissue itself. If the amount be small, it may be removed in many instances with the nail of the index-finger, which is introduced behind and above the palate and used to scrape the nasopharynx thoroughly. The finger should be protected with a suitable finger-stall in rubber or metal, and the hand washed with soap and water and bathed with alcohol before its introduction. The child's head is bent forward over a proper receptacle, and after the scraping is finished (which takes only a few moments) the child is urged to blow the resulting blood, mucus, and shreds of adenoid tissue from the nose, and also to expectorate them from the throat.

Frequently such an operation as this is insufficient or not indicated, and to establish a complete cure a specialist's operative treatment should be secured. This means preferably the use of Gottstein's curette or of some form of forceps, usually aided by means of more or less profound local or general anæsthesia with cocaine, nitrous oxide gas, bromide of ethyl, chloroform, or ether.

The presence of the so-called hypertrophied lingual tonsil or lymphoid tissue, which frequently enlarges in front of the epiglottis in the glosso-epiglottic fossa and encroaches upon the larynx, is often ignored or improperly treated. Many times already I have seen cough—irritative, ineffectual, obstinate—thus occasioned. Cough-mixtures, inhalations, sprays, are relatively useless, and even climatic changes, cod-liver oil, etc., are ineffectual to cause notable amelioration in this local state. In many instances, however, this tonsil becomes acutely inflamed and swollen, and when such is the case it is without doubt produced by a rheumatic or gouty dyscrasia. To ignore the use of the salicylates and colchicum means either no cure or surely a very protracted one.

Whenever the tonsil is chronically enlarged and occasions globus hystericus (so-called) or choking sensations and a constant tickling and irritation in the throat near the larynx, recourse must be had first to local applications of iodine, carbolic acid, or iron. If these fail, repeated applications of the galvano-cautery will ultimately afford permanent relief in many instances. In the most severe cases ablation by means of Chapelle's tonsillotome or some similar instrument is our sole available and suitable resource. Under these circumstances specialists' services are usually required.

Take, now, numerous examples of laryngitis, acute, subacute, or chronic in nature. Is there no such disease as an acute inflammation of the larynx? One bold specialist of wide renown has almost dared to affirm it. So convinced are some laryngologists that acute laryngitis proceeds from and is almost wholly caused by inflammation or obstruction of the nasal passages that they give the larynx itself little or no treatment—local or general—and yet how erroneous such views are. I am here prepared to affirm, and I still believe, there is such a disease, and a tolerably frequent one, as acute laryngitis. I believe it may be intercurrent with inflammation of the nose, pharynx, trachea, and bronchi. I believe it may be limited in a great degree to the larynx itself, and in either case be in no sense dependent upon the intranasal condition. I believe, also, that there are numerous instances in which the acute laryngitis is preceded by nasal and pharyngeal inflammation.

In many examples of acute laryngitis I should consider myself derelict in the highest degree if I did not combine general and local medication. When, however, we come to the treatment of the subacute form of laryngitis of simple catarrhal or inflammatory type, here I rely mainly upon the use of local applications of iron, iodine, zinc, copper, and carbolic acid, aided with mild antiseptic sprays. If the catarrhal condition continues or extends to the trachea or bronchial tubes, I feel called upon to make appeal to anticatarrhal agents internally, among which I rank ipecac, ammonium salts, and beechwood creosote highest.

If the laryngitis be chronic, and either the syphilitic or tubercular nature of it be suspected or confirmed, we must combine appropriate local and general means to attain the best results of treatment. In order to follow up such cases intelligently and judiciously we should make frequent, skilful use of the laryngeal mirror and the armamentarium of the well-informed laryngologist.

Is it wisdom to inject the soft parts with antiseptic preparations or scrape out ulcerated tissues and apply painful caustics in order to effect beneficial local changes, if possible, of laryngeal tuberculosis? I believe not, in the large majority of cases.

My conviction in this matter exists because, as a rule, the concomitant intrapulmonary condition is of such a character—of such an advanced stage of tuberculization—that I regard it as almost

criminal to make a poor sufferer submit to additional pain for a prospective gain of little or no practical value. Still, there are a few exceptions to this rule. Krause and Heryng have reported, as we know, some very brilliant results from active local interference, and he would be an ignorant or unwise practitioner wholly to disregard them in all cases.

In syphilitic stricture or stenosis of the larynx or nasopharynx it is not broad-minded to ignore what intubation or palliative dilatation may be able to accomplish in the way of relieving constant distress. Here, again, the specialist has his *rôle*, and a valuable one it is, to help us ameliorate otherwise hopeless cases.

I might prolong this paper unduly. I have written sufficient, I trust, to open a fruitful and interesting discussion of a practical and important subject. In no branch of medicine are the contrasts more frequent and essential between the general practitioner and the specialist than in what pertains to the wisely governed treatment of many affections of the upper air-tract. I am one of those who have always held— who still holds—that the clinician, the general practitioner, should usually—not to say always—control the specialist in all branches of practical medicine. I do not mean to affirm that the clinician should invariably and always treat the patient himself. I do say he should be the guiding hand—the one whose province it is to say, in most instances, to what extent it is wise and considerate for him to pursue particular lines of work.

NERVOUS DEAFNESS IN DIPHTHERIA.

By J. C. WILSON, M.D.,
OF PHILADELPHIA.

I REPORT the following case at some length, first, because sudden bilateral total deafness in diphtheria is exceedingly rare; secondly, because of the importance of this complication; thirdly, as illustrating the rapid disappearance of a tonsillar false membrane after the administration of an efficient dose of diphtheria antitoxin serum; and, finally, because it illustrates some phases of uncertainty in regard to the diagnosis of membranous sore-throat.

CASE. *Follicular tonsillitis in an adult; moderate fever, occipital headache, tinnitus aurium et cerebri; fourth day, dense pellicular exudate upon tonsils, conjunctivitis, increasing tinnitus and deafness, injection of diphtheritic antitoxin serum; a few hours later, total deafness with slight vertigo, great chemosis of the conjunctivæ; gradual defervescence, completed by the fifteenth day, at which date there was partial paralysis of accommodation, together with paresis of extensor muscles of the head, persistent tinnitus, slight vertigo, and absolute persistent loss of hearing.*—A married woman, thirty-three years of age; the mother of three children, the youngest being about seven years old; a private patient; was first seen in present illness November 12, 1896. She complained of sore-throat, which had begun the previous evening. Upon inspection there was observed general redness of the velum, half arches, and tonsils, with swelling of the last more marked upon the right side. Upon the right tonsil there were eight or ten small, discrete, grayish-white patches about 2 mm. in diameter. The exudate composing these patches was with some little difficulty detachable from the surface of the tonsil, and evidently occupied the openings of certain of the crypts. The other tonsil was free from exudate. The patient complained of pain on swallowing and headache, most intense in the occipital region. The temperature was 103° F. The treatment consisted in the administration of $\frac{1}{75}$ of a grain of calomel, 1 grain of Dover's powder, and 2 grains of caroid every hour, together with the use of a gargle consisting of equal parts of a 15-volume solution of hydrogen dioxide and cinnamon water, and the local application of hydrogen dioxide solution, full strength,

once a day, by means of a cotton carrier. On the following day the condition of the throat was much the same save that the grayish-white patches had entirely disappeared from the right tonsil, while similar patches had shown themselves upon the left tonsil.

Nov. 14th. Throat less painful; swallowing less difficult; headache has disappeared. Temperature, A M., 100.4° F ; P.M., 100°. Treatment continued, the powders being administered at intervals of three hours. Hearing impaired; the patient complains of distressing tinnitus, referred to both ears and to the head generally. On inspection of the throat there is seen a slight uniform, grayish film, about 1 cm. in diameter, upon the lower portion of the right tonsil.

15th, 8 A.M. The patient had passed a restless night, suffering from constant and distressing roaring in the head and ears. The temperature had fallen to 97° F. There was marked and painful conjunctivitis, the vessels being deeply injected. The greater portion of the right tonsil was covered with a dense grayish-white exudate, the borders of which were abruptly marginate, surrounded by a deeply hyperæmic zone. A similar though less extensive exudate had formed upon the left tonsil. Restlessness, constant nausea, occasional vomiting. The patient complains of pain in the eyes; rapidly increasing deafness and distressing sounds in the head, like bands of music, fire-engines, etc.

At 10 A.M. the temperature had risen to normal. Diphtheria antitoxin serum (Behring), 1500 antitoxin units, was injected into the right interscapular space. Treatment: small doses of calomel, alternating with tincture of the chloride of iron and a laxative enema; alcohol in the form of milk-punch and champagne. As a hypnotic, chloral in 15-grain doses at night. For the eyes, a weak alkaline lotion. Locally, hydrogen dioxide solution applied with a cotton carrier, full strength, every hour. At this time a culture was made and forwarded to the bacteriological department, and notification of the case as one of diphtheria sent to the Board of Health.

At 2 P.M. vomiting ceased and did not recur.

At 5 P.M. total loss of hearing. At this time great conjunctival chemosis, the œdematous conjunctival tissues rising prominently above the corneal margins and preventing the approximation of the edges of the eyelids. No pain in or about either ear, nor tenderness upon pressure. Temperature, P.M., 100.8° F. Urine: specific gravity, 1022; a trace of albumin; no casts.

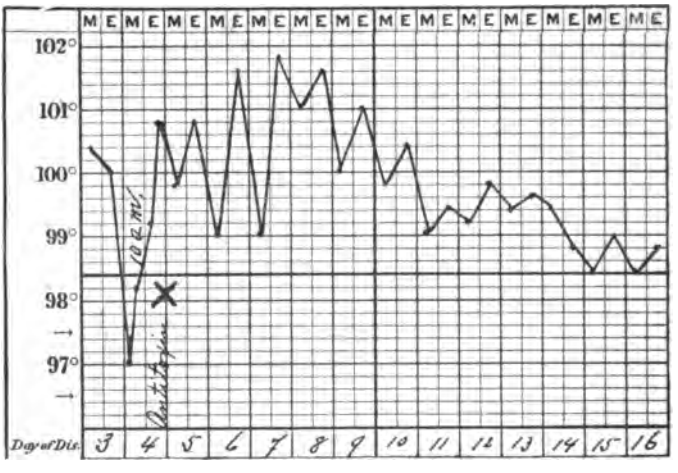
16th. Conjunctivitis more intense; condition otherwise the same. The Inspector of the Board of Health placed upon the front door of the house the usual poster indicating the existence of a case of diphtheria within.

17th. Membrane in the throat has disappeared. The patient had a more comfortable night and slept several hours. Upon examination the tympanic membranes are bright red, but glistening and not bulging. The report of the Board of Health received. The bacteriological investigation failed to show the presence of the Klebs-Löffler bacillus. Some doubt as to bone-conduction, the patient being unable to discriminate positively between

auditory sensations and the vibrations of the tuning-fork. Eyes treated by cold compresses.

18*th.* Bowels freely moved by enema. Large quantity of mucus in stool. Upon examination in a vessel of water sheets of pseudo-membrane and a tubular cast. The patient not known to have previously suffered from membranous colitis. Albumin has disappeared. The patient seen in consultation by Dr. S. MacCuen Smith, who visited her from time to time subsequently. Later she was also seen by Dr. Charles H. Burnett. Neither at this time nor at any subsequent period were there evidences of inflammation of the *middle ear*. From this time for a period of a week free sweating was induced every day by a hypodermic injection of pilocarpine. Upon notification of the negative report from the bacteriological laboratory the Board of Health caused the yellow poster to be removed from the front door of the house.

19*th.* Loss of power in the muscles of the back of the neck. The head falls forward and rolls to either side. Tinnitus continues.



Temperature chart.

20*th.* Free movement of the bowels, with a large quantity of stringy mucus.

29*th.* During this period the chemosis has gradually subsided, and the eyes are now practically well. Patient thinks she can hear the street-cars and wagons, but upon careful testing it is evident that she perceives only the vibrations of heavy vehicles passing. Up to this time her power of modulating and otherwise regulating her voice has been very imperfect. Some gradual improvement in this respect noted.

Dec. 4*th* The patient able to be out of bed for a few moments. Station only slightly impaired. Very moderate dizziness. Deep and superficial reflexes unimpaired. General nutrition improved. Tinnitus still constant and

distressing. It is referred now chiefly to the ears. The membranous colitis treated by daily high enemata of silver nitrate 1 : 1000. The tincture of the chloride of iron discontinued, the compound syrup of the hypophosphites being given in its stead, together with arsenic in the form of Fowler's solution. The membranæ tympani present a normal appearance, the redness having entirely disappeared.

16*th*. At the suggestion of Dr. Burnett the method of Lermoyez was employed, with the view of determining whether or not the deafness was due to anæmia of the internal ear. This method consists in the administration, by inhalation, of amyl nitrite. Five minims were poured upon a towel and held to the patient's mouth and nose. Intense flushing of the face immediately followed, the patient at the same time crying out, "Oh, my head!" and stating that the roaring, which had been confined to the ears, was now felt over the whole head with unusual violence. Her condition was most distressing, but passed off in the course of eight or ten minutes. The test was repeated a few days later with the same result.

It was noted upon the 20*th* that the noises in the head were much louder. They were described as being like the sound produced by the tearing of muslin, fire-engines, car-bells, and the like. The patient is now slowly acquiring the sign alphabet of the deaf and dumb. Communication with her is conducted by writing. She complains of difficulty in reading, and now suffers much from headache.

On the 28*th*, station was much more impaired than at any previous time, and there is distressing vertigo with headache. This condition continued for three days and passed off after brisk purging. The indications of membranous colitis continue.

29*th*. Blood examination by Dr. F. A. Packard, who made the following report: 5,025,000 red blood-cells, 1 white to 301 red. Hæmoglobin 70 per cent. Differential staining shows no abnormality.

The patient occasionally complains of double vision.

February 24*th*. The condition of the patient has gradually improved. The double vision has disappeared, the difficulty in reading diminished. Annoying tinnitus continues, together with slight vertigo and disturbance of equilibrium. The muscles of the back of the neck continue to be paretic. Deafness remains absolute, both to ordinary sounds and the tuning-fork held in contact with the skull. The patient can now distinguish between auditory sensation, which she cannot hear, and the vibration of the tuning-fork, which she readily perceives.

Dr. de Schweinitz about this time examined the patient, finding no lesion in the eye-ground, except a slight œdema of the retina and paresis of the ciliary muscle amounting to a loss of about one-third of the accommodative power.

At this date the patient went to Florida, where she spent some weeks, improving in every respect, and in particular wholly recovering from the membranous colitis.

Total deafness, annoying tinnitus, slight vertigo, impairment of station,

and paresis of the extensor muscles of the head persist at the present time (*May 1st*). The patient has only of late realized the nature of the misfortune that has befallen her in the loss of hearing, and has become apathetic and depressed.

The patient comes from a long-lived race on both sides. The father is living at the age of seventy-three years, but suffers from advanced interstitial nephritis. The mother is gouty and has gouty kidneys. There are two brothers and one sister in good health. One sister died of some acute septic process following confinement. The patient has never had syphilis; this subject has been very carefully investigated. She is a perfectly well-balanced, reasonable woman, with a good nervous system, and has never shown the stigmata of hysteria. The possibility of hysterical deafness may be dismissed from consideration.

Notwithstanding the negative report from the bacteriological laboratory, it is assumed in the title of this communication and in the discussion of the case that the disease was diphtheria. That it was clinical diphtheria is beyond question. The nature of the throat lesion, the character of the exudate developing after local lesions presenting the phenomena of lacunar tonsillitis, the rapid disappearance of the pellicle, leaving superficial erosions, after the injection of antitoxin serum, the impairment of accommodation and the double vision, together with the loss of power in the muscles of the neck, fully justify the diagnosis. Whether the bacteriological diagnosis failed because of the local treatment prior to the making of the culture, or not, cannot be known. The negative report from the Board of Health permitted the removal of the yellow poster from the front door of the house, and no further attempts to establish a bacteriological diagnosis were deemed expedient, however interesting they might have been from a scientific point of view. Nothing would have been gained with reference to prophylaxis, seeing that the patient was placed in an apartment by herself, was attended constantly by a thoroughly trained nurse who held no communication with the rest of the household; that the children and junior members of the family were immediately sent away; that systematic disinfection was practised throughout the course of the attack, and that immediately upon the patient's recovery the rooms which she and her nurse had occupied were disinfected with the formaldehyde apparatus by the Board of Health. No case of

disease traceable to this patient developed in any member of the household or any visitor.

Quite recently, at a time when it seemed to me desirable to place this case upon record, I communicated with Dr. Abbott, the medical officer in charge of the bacteriological laboratory, with a view of obtaining a fuller report, but learned that the slide upon which the report was based had been destroyed.

Sudden loss of hearing occurs after mumps, epidemic spinal meningitis, and during secondary syphilis. It indicates a lesion of the eighth nerve, either in the brain or in its peripheral distribution.

Buck[1] makes the statement that "if with the loss of the hearing there are associated the symptoms of dizziness, marked subjective noises, and a staggering gait, the diagnosis of an auditory nerve-lesion, probably labyrinthine, may be assumed with a good deal of confidence."

Hovell[2] states that "absolute deafness is pathognomonic of diseases of the labyrinth. It is very rarely met with, for there are few patients who are utterly unable to perceive sonorous vibrations conducted through the bones of the head."

In point of fact, an examination of the literature, necessarily cursory, leads me to believe that sudden, total, permanent, bilateral deafness is extremely rare, and I have been able to find no case in which it has occurred in diphtheria. A friend who has been kind enough to look through the entire series of the *Annales des Maladies de l'Oreille, etc*, covering a period of twenty years, has found no such case.

Gruber quotes Moos,[3] who reported:

"The conditions observed in the temporal bones of three children who died from simple diphtheria, and in which the middle ear exhibited merely catarrhal changes. They were similar to those found in the labyrinth by Steinbrugge in cases of epidemic cerebro-spinal meningitis. The membranous semicircular canals were in many places partially or entirely filled up by a substance consisting of coagulated lymph and a large number of cells with one or more nuclei. The mass exhibited concentric stratification and more or less advanced development in the direction of connective tissue, bone, and bloodvessels, and was here and there adherent to the periosteum.

[1] Manual of Diseases of the Ear. Second edition, 1895.
[2] Treatise on Diseases of the Ear, London, 1894.
[3] Gruber: Text-book on Diseases of the Ear. Second edition, English translation, 1893.

. . . The bloodvessels were obviously congested, with rupture and extravasation of blood, thus producing breaches of continuity in the courses of the auditory nerve."

Loss of the osseous substance and invasion of the cancelli of the petrous portion of the temporal bone by chains of micrococci were noted.

No evidence of osseous lesions have been seen in the case that I report.

With reference to the importance of total bilateral loss of hearing as a complication of any of the acute diseases little is to be said. The remote possibility of such an accident adds greatly to the gravity of any acute disease.

It is necessary to speak definitely with reference to the administration of the diphtheria antitoxin serum in this case. This was done within a few hours of the recognition of the conditions justifying a clinical diagnosis of diphtheria. No reaction at the point of injection occurred. The temperature, which had been very low and was rising at the time of the injection, continued to rise slightly for a few hours. It is probable that the antitoxin had no effect upon the temperature whatever. The following day the general injection of the throat was less marked, and within forty-eight hours the false membrane from both tonsils had wholly disappeared, leaving superficial erosions, which rapidly underwent cicatrization. It is important to observe that on November 14th, twenty-four hours prior to the administration of the antitoxin serum, it was noted that the hearing was already impaired, and that the patient complained of distressing tinnitus, referred to both ears and the head generally.

The antitoxin serum exerted an obviously favorable influence upon the condition of the throat, but failed to arrest processes involving the labyrinth and the subconjunctival lymph-spaces that had already made some progress.

DISCUSSION.

DR. BEVERLEY ROBINSON: I rise to make two or three points. The case is interesting from several points of view and because it is reported in the fullest details. But from another standpoint it is far more interesting.

The practitioner is placed in a false position in these cases. The first instance was that of a child whom I was called to see at 2 o'clock in the afternoon. The child had complained on the previous evening of a sore-throat and a general condition of depression, which alarmed the parents. I found a membrane in the throat which had every clinical evidence of being diphtheritic. I took a swab and sent it to the Board of Health for examination, and within two hours the child was injected with a proper amount of antitoxin-serum. The Board of Health reported that it was dissatisfied with the culture taken from the throat, and wanted another culture made. I took another swab and sent it to the Board of Health, and they again reported that they were dissatisfied and wanted another culture made. This was done, and a third report was received, saying that it was not diphtheria. Nevertheless, I have always regarded the child as having had diphtheria, in spite of the report of the Board of Health to the contrary. My point is this: that we may be called to see a child and find it with symptoms pointing to diphtheria, and we ask ourselves the question, Shall we inject antitoxin or not? If we do so, we may have later a report from the Board of Health saying that the case is not diphtheria; and if we do not, but wait until we can hear from the Board, we may do harm by delay in making our antitoxin injection, supposing that the case is one of diphtheria.

Another point which I wish to make is, that while it may have been very gratifying to Dr. Wilson and myself to have reports from the Board of Health that our cases were not diphtheria, because the parents were then not required to label their houses and run to tell the neighbors, we continued to treat them precisely as if they were diphtheria. From the point of view of practitioners of medicine, we must lay more stress upon the clinical aspects of a case rather than on the pathological. There are a certain number of gentlemen who, for the time being, may be very skilful in the latest methods of bacteriological examinations, but who have not seen the patient, and they cannot possibly know as much about the case as those who have seen it.

I was glad to hear our distinguished colleague, Dr. Janeway, when referring to the serum-test for typhoid fever yesterday, say that for the first few days we must not neglect to treat all suspicious cases as typhoid, even if the test were negative, and perhaps a few days later we would have an undoubted case of typhoid.

DR. I. E. ATKINSON: It is manifest that when we have clinical evidences of disease and negative results of bacteriological examinations are obtained, it is necessary to look very closely and see whether all the conditions have been fulfilled. In cases of suspected diphtheria, where the Klebs-Loeffler bacillus is wanting, the question arises, Is there not some other way of accounting for the symptoms? It is not impossible that this case may have been some form of septic infection. The result is similar to what sometimes follows cerebro-spinal meningitis. The following case will illustrate the dependence upon sepsis of symptoms that might readily have been mistaken

by the clinician for those dependent upon and consequent to true diphtheria. An infant of fourteen months was seized with a mlid eruptive fever, which the physician in attendance diagnosticated as scarlatina. The fever was so mild, and the eruption so slight and transitory, that the family refused to accept the diagnosis and to isolate the child. After a few days a membranous pharyngitis and stomatitis of great extent and intensity developed, and the fever at once became very high. Cultures developed not the Klebs-Loeffler bacillus, but staphylococcus aureus, and justified the diagnosis of scarlatinal membranous pharyngitis. The child was treated with cold baths, by means of which the high temperature could be readily reduced, only to recur again within a very short time. Septicæmic symptoms speedily developed. Cerebral symptoms, with strabismus, convulsions, spastic contractions, etc., indicated a meningitis. Colitis and middle-ear inflammation, with perforation of both drums, septic cutaneous eruptions of the urticarial and erythema-multiforme type developed, and the child was brought to the very brink of death; but after ten days began gradually to improve, and finally convalesced. In the absence of the Klebs-Loeffler bacillus the possibility of milder or graver forms of septic infection should be considered in obscure cases. I would hesitate to accept Dr. Wilson's patient as suffering from a sequel of diphtheria in the absence of the specific bacillus and in the possibility of ascribing the symptoms to other influences.

DR. M. HOWARD FUSSELL: A girl last fall had a sore-throat, and a bacteriological examination showed diphtheria bacilli. The case recovered in two or three weeks and was dismissed in proper time. After dismissal she was brought to my office with complete loss of accommodation. A careful examination also showed that her hearing was reduced to four inches by an ordinary watch. The paralysis of accommodation was proved by an ophthalmologist. She was given strychnine, and to-day, six months after, there is no paralysis; she hears well and sees well.

DR. W. W. JOHNSTON: This is indeed an era of anomalous cases. Recently, within a few years past, we have become well acquainted with a disease that is accompanied with very varied lesions and with symptoms connected with every organ of the body; I mean, of course, epidemic influenza. Dr. Atkinson's case, which he attributes to septic infection, resembles in many respects a form of influenza; and Dr. Wilson's case is, I believe, capable of the same explanation. The failure to find the bacillus is a missing link in the chain of evidence, and the anomalous and unusual symptoms increase the doubt as to its diphtheritic nature.

DR. J. C. WILSON, in closing the discussion, said: I fully appreciate the views expressed by Drs. Atkinson and Johnston. I am aware that there is a link missing in the demonstration of my case. I hold, however, in the first place, that while recognizing the uncertainties of a clinical diagnosis in

some instances, we are not compelled to go out of our way to make a diagnosis of some uncertain infection, as suggested by Dr. Atkinson, on the one hand, or of influenza, as suggested by Dr. Johnston, on the other; but that we are practically forced to take the only direct way that would have been open to us a few years ago, and that, in this instance, is to the diagnosis of diphtheria. We have all seen innumerable cases of influenza in recent years, many of them in the highest degree anomalous; but I certainly have never seen a case of influenza with the definite, consecutive train of symptoms, especially those relating to the nervous system, seen in this case—symptoms seen almost every day in diphtheria. I have reported the case, notwithstanding the point that has been criticised, on account of the labyrinthine disease and the total permanent loss of hearing—a condition of the rarest in acute diseases. With reference to a clinical diagnosis, I am something of the same way of thinking as Dr. Robinson. In a case where the clinical diagnosis is obvious, but the diagnosis made in the laboratory is uncertain, I hold that the burden of proof rests with the worker in the laboratory, who has not seen the case.

A FURTHER COMMUNICATION ON THE OCCURRENCE OF A HITHERTO UNDESCRIBED FORM OF CHRONIC NEPHRITIS UNASSOCIATED WITH ALBUMINURIA.

By D. D. STEWART, M.D.,
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In two previous communications on this subject[1] I drew attention to a small group of personally studied cases of evident chronic nephritis, in all of which, with quite similar clinical characters, the urine was persistently albumin-free during the period in which they were under observation. I regarded these cases as representing, perhaps, a not uncommon, although hitherto unrecognized, variety of nephritis, the symptoms of which in all agreed more or less in certain important particulars. The character of these were such, I remarked, as to place them clinically without the boundary of the well-known varieties of the so-called Bright's diseases, such as chronic desquamative nephritis and the fibroid or granular kidney.

Concerning the absence of albumin in chronic nephritis, I pointed out that it had been long known that cases of fibroid kidney could occur, especially in the early stages of the malady, without albumin in the urine, or with albumin existing, if constant, only in traces, or to be found in certain portions of the twenty-four-hour urine. I said that "the occurrence of typical granular kidney without albuminuria had been first noted by Wilkes, of Guy's Hospital, nearly half a century ago, but it was Mahomed, some three decades later, who especially investigated cases of this phase of the disease, de-

[1] "On the Occurrence of a Form of Chronic Bright's Disease Other than Typical Fibroid Kidney, without Albuminuria," Transactions of the First Pan-American Congress, and the American Journal of the Medical Sciences, December, 1893. "Further Remarks on the Occurrence of a Form of Non-albuminous Nephritis Other than Typical Fibroid Kidney," Transactions of the College of Physicians, 1894, and the Medical News, April 14, 1894.

scribing a considerable number of them in *Guy's Hospital Reports* for 1879 and 1880-'81. But it was doubtful if many of Mahomed's cases, such as I cited, were actually cases of renal disease, though they could be properly included in the category of chronic Bright's disease as Mahomed employed the term. The symptoms of numerous of these were in the main referable to other organs, and in a minority of those in which a necropsy was obtained the kidneys were stated to be normal.

I pointed out that

"Mahomed had adopted the term chronic Bright's disease as a convenient generic name for a condition which Gull and Sutton had previously described of generalized arterio-capillary fibroid change. Contrary to the view of Johnson, an extension of that of Bright, and following in the lead of the above-mentioned investigators, Mahomed viewed the condition underlying the various stages of granular or fibroid kidney as a systemic disorder, in which the cardio-vascular alterations were not dependent upon, but either antedated the development of the kidney fibrosis, or more rarely existed without renal change. It was not necessary for him that the kidney be the seat of degeneration to constitute Bright's disease. Fibroid kidney was but an unnecessary, if more or less to be expected, incident in the general morbid state. Renal fibrosis did not always appear, though general arterial change occurred."

I further observed that

"Apart from the doubtful cases of renal disease among those reported by Mahomed, in which albuminuria was absent, there remains a good number in which, with the urine free from albumin, undoubted granular kidney existed. Be that as it may, Mahomed's cases were all in middle or advanced life. There were present decided cardio-vascular changes, such as hypertrophied heart and thickened vessels. These cases were reported especially to show that in the stage of Bright's disease in which epithelial alterations in the tubules were absent—or, if occurring, were but transitory in character—albuminuria was absent, the urine remaining practically normal, and symptoms referable to the kidney—*i.e.*, those of renal inadequacy—were uncommon. Death in these cases, as Mahomed remarks, is usual in granular kidney, resulted from failure of other organs, notably the heart."

This class of cases described by Mahomed, I said,

"Related only to the typical arterio-capillary fibroid kidney so ably portrayed by Sir William Gull: an affection occurring in the degenerative period of life, and part and parcel of a diffused cardio-vascular decay. In this class it is well recognized that with an accompanying polyuria, or with urine, less commonly, perhaps, unaltered as regards amount, the ex-

cretion of urinary solids, especially the nitrogenous, is often not far from normal, as in these the histologic renal changes may be but slight in character, the secretory structure not being sufficiently implicated to show marked deviation from healthy function. When such deviation, however, becomes apparent, it is likely to be coincident with the appearance of decided amounts of albumin and of casts in the urine, with dropsy and marked uremic symptoms."

Cases of chronic nephritis occurring other than at the degenerative period of life, in which, without evident indications of accompanying arterial sclerosis, and in which the symptoms were so frankly of kidney origin as to indicate that the affection was beyond everything else a primary renal disease, to which changes in the vascular system were subsidiary and in all probability a result of a toxic blood state induced by the imperfect functioning of the damaged kidneys, were not recognized by Wilkes or by Mahomed, and their even rare occurrence is still regarded by many as apocryphal. If such a case with pronounced symptoms is accepted to be one of nephritis, it is commonly thought that the absence of albumin, if such is proved, is either an ephemeral condition or that the ailment as yet is too limited in its seat and too early in its course for albumin to appear. It was to such cases as these that I especially directed attention, reporting a small group in which the symptoms were so distinct and separable from those of the well-recognized forms of nephritis as to indicate for it a distinct pathology.

As to these symptoms I stated that

"With an oliguria as persistent and as marked in certain cases as in the most outspoken type of chronic parenchymatous nephritis, and with a urine as concentrated, yet with absence of cardiac debility and of dropsy to indicate its source, there occur as grave continuous symptoms of renal inadequacy—those, indeed, of pronounced uræmia. These are associated, too, as in chronic parenchymatous nephritis, with as marked diminution in urinary solids, notably diminution in urea and mineral ingredients, indicating undoubted secretory involvement; yet totally unlike what is distinctive of parenchymatous nephritis, albumin is so persistently absent from the urine, even with the existence of the aggravated symptoms of renal incompetency, as to clearly indicate that its presence need form no part of the assemblage of symptoms or have any relation to the morbid condition."

In describing these cases to show that albumin need not necessarily appear in the urine even in an advanced stage of chronic nephritis, and that death from uræmia may occur without its presence, I cited

a most interesting case, the history of which was furnished me by Dr. C. A. Oliver—a case, the clinical character of which suggests that it belongs to the class, I have described.

The patient, Miss X., nineteen years of age, an apparently strong and healthy girl, of refinement and education, without hereditary taint of syphilis or gout, was referred to Dr. Oliver by the attending physician for eye examination, a refractive error being suspected, because of severe recurrent headache, which had existed for some time. Examination of the fundus oculi disclosed a beginning undoubted retinitis Brightii. The urine was now examined carefully and repeatedly up to death, which occurred seven months after she was first seen by Dr. Oliver. The examinations were made not only by Dr. Oliver, but by especially trained experts. It was persistently albumin-free throughout the time the case was under observation. Death suddenly resulted from uræmia. An autopsy, according to Dr. Oliver, showed granular kidney.

In this case, as in those I detailed, the urine was of normal specific gravity. As to the average quantity commonly voided in the twenty-four hours, I was not informed, but from the usual specific gravity being 1020, there was little doubt that it was diminished. I also briefly referred to cases in which death occurred, reported by the late Millard, in which albumin, though frequently examined for, was at no time found. One of these cases was shown post mortem to be interstitial nephritis with a limited glomerulonephritis. In the other, a male, aged twenty-three years, the chief clinical symptoms were pronounced debility, persistent headache, and nausea. There was hypertrophy of the left ventricle, but no indications of œdema. His appearance was sallow and anæmic. Suddenly convulsions, succeeded by coma, resulted in death. The urine was totally free from albumin during the time the case was under observation. Casts and renal epithelia were present. Although no autopsy could be obtained, the indications were quite certain that the case was one of nephritis.

There must exist some radical pathological difference in the renal condition of such cases and those in which, whether with or without the presence of albumin in the urine, but with the constant occurrence of casts, and more or less steady diminution in the excretion of urea, symptoms of retention of nitrogenous waste are totally absent, even though there may be present a typical retinitis Brightii, indicating that the disease is in an advanced stage. I recently studied

several cases of this sort for Dr. L. Webster Fox, in three of which symptoms referable to the kidney were totally absent. Headache did not occur, vertigo was uncommon, and the general health was quite well preserved. The patients regarded themselves as in good health, apart from failing vision. In all Dr. Fox had encountered what he termed "non-albuminuric retinitis." In one case "the right eye was a mass of retinal hemorrhages, with here and there colloid degeneration, so characteristic of M. B.;" in the other cases a quite similar retinal condition was evident. Albumin had been found absent in a number of examinations made both by Dr. Fox and the attending physician of the cases. In the urine of one of the three I found in several examinations a trace of albumin; this was evident to the heat-test, and trichloracetic acid gave an instantaneous sharp ring. In the others traces of albumin were absent to heat. These cases clinically rather fell into the category of those described by Wilkes and by Mahomed, in which, perhaps, with extensive renal fibrosis, the excretion of toxic products was not far from the normal.

Of the personally studied cases I reported, unfortunately but one has remained under observation to the present. The others were studied for one month in one case; three months in another, to from six months to four years in the remainder. Whether any of those that disappeared from observation have died in the interim, or, if living, changes have occurred in the character of the symptoms, in all save one, a brother of the case specially detailed, is quite unknown to me. Of the pathological conditions in the kidney of this case (Case II. of the series described) I am able to make a report. This is of special interest, since the case may be regarded to be clinically a good example of this group.

The patient is J. B., aged thirty-four years.[1] First came under observation in the early part of 1893. Symptoms of his ailment had then existed for about two years. These were, briefly, more or less severe headaches and spells of vertigo; there had been from the first more or less prostration of strength, with incapacity for physical or mental exertion. This physical weakness has greatly increased in the last two years. But slight continuous exercise of mind or body induces severe headache, with vertigo and

[1] For more detailed history of this case see the American Journal of the Medical Sciences, December, 1893, p. 665.

a sensation of great body weariness. There has been a tendency to more or less loin tire, and often to actual ache. There is also disturbed sleep, during which night-terrors are common and limited clonic spasms occur. The blood-pressure is habitually very high, the sphygmograms showing always a pulse of markedly raised tension.

During the early period in which he was under observation a strictly vegetable diet, on which he was placed for a few weeks, greatly lowered blood-pressure so that it became practically normal. This diet could not be continued on account of the dyspeptic symptoms originated by the food, and the marked oxaluria so induced.

The patient had lost twenty pounds in weight during the first two years of his ailment. This loss has not been regained. There has been no decided anæmia evident. Blood examinations made at intervals commonly show a nearly normal blood-count. The skin is more or less habitually dry, and the complexion the past three years has been of a decidedly sallow hue.

Debility, headaches, and vertigo were so prominent in this case, and these and other symptoms were always so aggravated on exertion that, although previously when in good health he had led a most active life, he has been compelled to abandon his pursuits, and become against his will a valetudinarian. Remedial measures have been of no permanent value for the relief of symptoms.

The urine has always been albumin-free to the present, excepting immediately succeeding the reni-puncture and excision of the small portion of the kidney. The urine has from the first been habitually much diminished in amount. When he first came under observation his habts were, as now, very methodical, and taking almost daily the same quantity of food and fluid, the urine, measured for seven or more consecutive days, at intervals of a month, stood steadily between 700 and 800 c.c. The past year between 500 and 600 c.c. are more common. The amount voided in twenty-four hours not being known, a single specimen as concerns color, specific gravity, and absence of albumin, would be regarded as normal. Even under thyroid extract and other remedies, the use of which tends to increase nitrogenous output, urea excretion had been very low, rarely exceeding 15 grammes. It commonly, estimated over long periods, runs between 13 and 15 grammes, about half the normal output for a person of his weight on the diet employed. Uric acid elimination is normal; at times it is a trifle high; the chlorides, as in all of these cases are, as with the urea, habitually diminished in amount.[1] Microscopically, the urine is found invariably to contain cylindroids, commonly in some amount. Hyaline casts are usual, and granular-hyaline, or finely granular, are not rare. Occasionally epithelial casts are found. Free uric acid and calcium oxalate crystals are common. As the specimens examined microscopically were commonly those of the mixed twenty-four-hour

[1] Diminished output of chlorine, in face of a normal or lessened HCl secretion, as had been ascertained in this and in several other of the cases, is of special significance, as was remarked in my previous paper.

urine, which had stood for some little time after voiding, the presence of these cannot be regarded as of significance. It is, however, a fact worthy of note that in all of these cases calcium oxalate and free uric acid crystals were frequently seen in the specimens examined shortly after voiding. Irritability of the bladder, such as is usual with a free output of uric acid and of the oxalates, has never been present. So much is this absent here that the patient not only never arises at night to urinate, but almost never empties the bladder oftener than two or three times in the twenty-four hours.

As in the other cases, albumin was never present in any of the examinations in amount to be detected by the application of the most reliable of all methods for its detection: heat, and the subsequent employment of acetic acid. By the more refined and less accurate tests, such as trichloracetic acid, the urine gave no instantaneous reaction. Commonly, with the employment of a super-saturated solution, a response only occurred at the expiration of from one-half minute to several minutes, and then was slight in character. This, as I have elsewhere shown, is usual in all normal urines. My own urine and that of several other healthy individuals working in my laboratory, often tested coincidently, commonly showed a more marked response to trichloracetic acid.[1]

Recently I was fortunate in securing a section from one of the kidneys in this patient for pathological study. This opportunity was suggested by the results obtained by Reginald Harrison in his cases recently reported, in which reni-puncture, and slitting a too tightly distended capsule in cases of extreme congestion of the kidney, occurring in the course of nephritis, had been followed by decided symptomatic relief. Although slight benefit was to be expected from such a procedure in this case, and but scant hope of it extended, the patient acquiescing, Dr. Keen exposed one of the kidneys, depleted it by spearing, slit the capsule, and subsequently removed a small section of the organ for histologic examination. The kidney was of normal size, but extremely hyperæmic. Despite this congestion, immediately before etherization a specimen of urine obtained was still found to be albumin-free, although cylindroids abounded and hyaline casts were moderately numerous.

For several weeks succeeding operation the urine contained albumin, as might be supposed. During this time there were abundant blood-corpuscles, blood-casts, and a profusion of epithelial, granular, and hyaline casts present in all specimens. The albumin gradually diminished in amount and finally disappeared at the end of a month. Although the patient was somewhat buoyed with hope, no benefit followed the operation. On the contrary, there has recently been an aggravation in his symptoms. The specimen removed was submitted to Dr. A. O. J. Kelly for examination. The following is his report:

[1] Many of the examinations in the past year in this case, both chemical and microscopic, were made for me by Dr. A. A. Ghriskey, to whom I am much indebted. It is needless here to describe the technique employed in the examinations for albumin in these cases. This is given in detail in my previous papers.

"The specimen was handed to me in 5 per cent. formalin solution, wherein it remained twenty-four hours before being inspected. It was then found to be of irregular pyramidal shape. Its greatest length was 2 cm., its greatest breadth 1.6 cm., its greatest thickness 0.6 cm. It weighed 0.3 gramme. It was transferred to alcohol, subsequently imbedded in celloidin, and sections made in the usual manner. They were stained with hematoxylin and eosin, hematoxylin, picric acid, and fuchsin, and likewise carmine. There are certain appearances which are the result of injury to the organ as the result of the operation; these are, chiefly, partial disorganization of tissue in portions of the section, with the presence of coagulated material in some of the tubules, the result of blood extravasation and the action of the hardening agent. These in no way interfere with or confuse the examination.

"The bloodvessels are distended and generally filled with blood. The intima in some few isolated places shows a slight proliferation of the endothelial lining. The media is thickened and stains rather homogeneously. It is, however, the adventitia that is especially involved. It is greatly thickened, and from it as a focus there proceed in various directions radiations of homogeneously staining connective tissue. In some places this perivascular connective-tissue overgrowth extends quite a little distance from the vessel, and it is here and there the seat of a slight round cell infiltration, though usually this is not evident and is never marked. This connective-tissue overgrowth is also present in areas in which no bloodvessels can be seen, but it is doubtless connected with bloodvessels that do not appear in the section. It is especially evident about bloodvessels in the neighborhood of the glomeruli. The capsule of Bowman is associated in the process; it is thickened and rarely, if ever, shows any cellular infiltration. Thus originating about the bloodvessels near the glomeruli, involving the capsule of Bowman, this sclerosis spreads to a limited extent and surrounds the uriniferous tubules in the neighborhood. The epithelial lining of the capsule of Bowman is frequently proliferated, and in some instances is free, doubtlessly artificially produced. Many of the convoluted tubules show a slight degree of degeneration; the epithelial cells are more granular than is normal; in many instances the lumen of the tubule is filled, and not rarely the nuclei stain imperfectly, exceptionally failing to take the stain at all. Not rarely formations resembling casts are seen. There are other more extensive areas of sclerosis in which the bands of connective tissue are much thicker, and in the midst of which the uriniferous tubules are smaller, not a few atrophic, and now and then one is seen obliterated. In a few places there is a very marked proliferation of the epithelial lining of the glomeruli and great thickening of the capsule of Bowman. From this latter the connective tissue overgrowth extends quite a distance surrounding the uriniferous tubules. The tufts of bloodvessels in the glomeruli are usually distended. In those glomeruli, however, about which there is such an excessive overgrowth of connective tissue they are diminished in size and at times quite atrophic. Exceptionally one notes a roundish area faintly fibrillar containing not a few slightly staining round

cells, the whole being suggestive of an obliterated glomerulus or blood-vessel."

Microscopic sections of the kidney were submitted to Prof. Wm. H. Welch, of the Johns Hopkins Medical School, who reported in substance that he could confirm Dr. Kelly's observations of chronic interstitial changes as stated. The changes, according to Dr. Welch, although of slight extent, were unquestionably evident, and consisted of new growths of connective tissue about certain of the bloodvessels and some of the glomeruli, with atrophy here and there of a few tubes and a few glomeruli. Here and there also he noted a slight thickening of the intima of the bloodvessels.

In discussing in my first paper the probable pathological renal condition which underlay these cases I remarked that although the assemblage of symptoms was typical of no distinct form of chronic nephritis, their trend was suggestive of granular kidney. But they had in common several points, the mingling of which in granular kidney has before been undescribed, such as absence of marked cardio-vascular change, and of dropsy, with habitual diminution in the amount of urine and in the urinary solids, and especially in urea, together with the presence of obtrusive signs of a toxic blood state. Unfortunately we know too little of the intimate physiological processes occurring in the kidneys in health and disease to more than conjecture as to the mode of production of symptoms from what to us is evident in the post-mortem condition.

Although the gross changes present in this kidney may not be regarded as sufficiently marked in any one direction to readily explain the symptomatic condition, they are, in certain particulars at least, suggestive. In first reporting these cases I remarked, as to the pathological renal condition, that there might be present glomerular changes of the nature of thickening of the capsule of the Malpighian tufts and of the afferent vessels, which could account for the diminution in the amount of urine voided, a symptom common in these cases, and not rare in others of supposed granular kidney in which dropsy is absent. Mahomed had thought that absence of albumin in certain cases of chronic nephritis might be due to a similar thickening of the vessels of the tufts, through which it would be difficult for albumin to pass, and also to thickening of Bowman's capsule, preventing distention of the vessels. It is significant, at least, that such thickening of vessels and of Bowman's capsule is, according to Dr. Kelly, usual in the specimen. Whether, however,

it exists to such a general extent as to cause obvious symptoms, otherwise apparently inexplicable, is questionable.

The absence of numerous granular, and especially of epithelial casts, was strongly against decided changes in the tubules, and yet, as in all, the habitual imperfect elimination in nitrogenous waste, with symptoms resulting therefrom, points strongly to alteration in the secretory epithelia of the tubular system, which changes, since not marked microscopically, must, perhaps, be rather of a molecular or biochemical nature.

Present indications support the view of Luff,[1] that a long-continued so-called functional affection of the epithelium of the convoluted tubules may antedate those cases of gout in which structural alteration in the kidney is not evident. This change, although molecular, may be none the less evident in its effect; a similar involvement of that part of the tubular system concerned in the elimination of these toxins the undue retention of which induces a uræmic blood state, may be the chief pathological condition underlying the symptoms in those cases of nephritis in which intoxication is evident without marked apparent implication of the secretory system of the kidney to account for the symptoms. So little is known of the intimate nature of the toxins inducing so-called uræmia, whether they are always similar poisons and not foreign to the organism in health, such as bodies allied to the xanthin group, the toxicity of which is little if at all apparent without damaged kidneys, because of its free elimination, or whether they be substances unknown normally, which are generated either in the kidney or on the other side of it, in the organism, from waste products in themselves harmless, is at present conjectural. Our knowledge is, indeed, but conjecture as to the mode of origin and manner of excretion of such waste products as urea and uric acid and the allied xanthin derivatives. At present the trend of evidence is in favor of the view that except in conditions of hyper-leucocytosis, uric acid is formed only in the kidney, and, perhaps, by the epithelium of the convoluted tubules, which is concerned, too, in its subsequent excretion. It is held on good evidence that uric-acid excretion is commonly deficient in gout and that its accumulation in the blood, through imperfect

[1] See "Gulstonian Lectures on the Pathology of Gout," British Medical Journal, April 3, 1897, p. 480.

elimination, is one of the causes of an outbreak of the malady. This is the view of Garrod, of Sir William Roberts, of Levison,[1] and others. This faulty elimination is now regarded as probably due in nearly all cases to preceding disease of that portion of the kidney concerned in the excretion of uric acid. Such changes, as have been said, are looked upon in certain instances as being at first merely functional.

As concerns intimate knowledge of urea formation and its mode of excretion, we are still somewhat in the dark. Apparently its seat of formation is the liver and its source the proteids of the food.

Some experiments I recently began (the details of which, as they are yet but in their incipiency, I shall not here give) as to the influence of urea ingestion on urea excretion, in the subjects of chronic nephritis, tend to show that diminished urea excretion in at least some cases of nephritis, and those, too, with frankly damaged kidneys, is not so much the result of urea retention as it is of deficient formation. If subsequent experiments support these results, the situation will be still more perplexing. This suggests either that the long-overtaxed, crippled kidney has gradually called a halt on urea formation in the liver, although the nitrogenous intake remained high, and the digestive condition for its transformation into soluble products, the supposed antecedents of urea, remains good, or that the kidney itself is at least somewhat concerned in urea formation, and that its seat of formation here, as with uric acid, may not also be the seat of its excretion.

The purposes of this paper do not permit of a discussion of these problems, which are mentioned here merely to point out our lack of knowledge of many points in the pathology of chronic nephritis. The most important practical point in the matter is the recognition of such cases as I have described, occurring as they do with an albumin-free urine, a single specimen of which, as regards absence of albumin and as regards color and specific gravity, might be viewed as normal. I need not here again call attention to the necessity

[1] Levison believes that renal diseases always antedate gout, and that such disease has its seat in the epithelium of the convoluted tubules. He holds that this portion of the kidney is the starting place of granular kidney, from which such interstitial changes as occur are secondary. Greenfield regards the glomeruli as the seat of the incidence of granular kidney, from which the degeneration in the epithelium of the convoluted tubules and the connective-tissue changes are secondary.

for searching microscopical examination of the urine for morphological kidney elements, which, steadily evident, cannot but indicate structural change. The constant presence of casts can have but one meaning when associated with imperfect elimination of urinary solids, such as urea, and with the occurrence of such symptoms arising from inadequate kidneys, such as headache, vertigo, debility, and persistent presence of raised blood pressure.

THE CUMULATIVE ACTION OF DIGITALIS.

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THE most important point in beginning this article is to consider what is meant by the "cumulative action of digitalis." By this term I mean the more or less sudden development of an irregular action of the heart in a person who has taken large and repeated doses of digitalis, with a corresponding irregular, hobbling pulse and, if the effects are severe, vomiting, feebleness, and a sensation of cardiac distress as additional symptoms. These symptoms may come on while the patient is lying still, but are more frequently initiated by the patient sitting upright or moving in such a way as to increase the work of the heart and vasomotor system. When bodily quiet has been maintained by rest in bed for some days or hours the onset is usually sudden, but when the patient has kept on his feet the symptoms may come on more gradually. These symptoms are apparently due to the fact that the drug is given in such amounts and so frequently that it accumulates in the body; or if the drug itself does not accumulate its effects accumulate, so that before the effect produced by one dose is passed by the effect of another is superimposed upon it.

In the belief that digitalis has this cumulative effect the writer of course does not stand alone, for nearly all authors speak of it, and many of the profession believe in the possibility of its occurrence even if they have not met with it. Thus, Soullier (*Traité de Thérapeutique et de Pharm.*, Paris, 1895) says that digitalis is one of those drugs which possess the curious phenomena of accumulative effect, which necessitates the suspension of the remedy for eight days after it has been given eight days, and quotes Lepine as never using it on consecutive days. Waring in his *Therapeutics* says

that digitalis when given in small, long-continued doses is apt to accumulate in the system and suddenly induce poisonous and even fatal effects

On the other hand, there seems to be some doubt as to whether we all have exactly the same idea of what we mean by this term, and some authors—and they are not a few—assert that a cumulative action does not occur. Thus Beaumont Small, in the *Reference Handbook of Medical Science*, supplementary volume, expressed this idea, and Bartholow "agrees in opinion with those who hold that digitalis is not a cumulative poison in the sense in which this term was formerly used." On the other hand, he admits that "doses of digitalis frequently repeated one after another, so that the effect of one is added to those before given, will certainly produce toxic symptoms," as will all other poisons used as medicines. It seems to me that this is to a great extent exactly what happens in those cases in which what I call "culminative effects" take place, and I do not believe that digitalis possesses any uncanny cumulative power of an extraordinary kind. On the other hand, I do not believe, not only from experience but from its known action given in small doses in all cases, that the ground for the assertion that digitalis is peculiarly apt to cause a cumulative result is very firm.

In the administration of remedies we are not sufficiently governed by the speed of their absorption and elimination, and particularly is this true of digitalis. Again, we are apt to overlook the fact that certain drugs produce an effect which is prolonged. This is also particularly true of digitalis, for not only does its influence last for several hours, but often for several days. Again, there are certain states of the body which hinder absorption for a time and delay elimination, and also prevent this drug from acting while in the blood; as gastric atony in the first case, renal spasm or disease in the second, and fever in the third. In other words, while it is true that any drug has a cumulative effect when given too often, it is also true that digitalis can more readily be given too often than many other drugs. Again, the very physiological effect of digitalis tends to make it accumulate, for as Brunton points out, digitalin when taken for several days causes a decrease in the flow of urine, and this is due to spasm of the renal bloodvessels, which may be so great as to cause suppression of urine. It therefore stands to reason that the frequent repetition of full doses

must lead to its accumulation in the body, for the supply is greater than the amount eliminated.

Such an accumulation with the production of a profound effect is met with when any drug which is slowly eliminated is given frequently in full doses; as, for example, in the case of bromide of potassium, where with each succeeding day and dose, the dose being the same, the sedative effects are more marked. Waring asserts that the bromides are sometimes taken in large doses for several days without effect, and thus a cumulative effect comes on. In this case, however, the effects are gradually increased, and the physician can measure the depth of the influence of the drug more accurately than when digitalis is given, for a peculiarity of the overaction of digitalis is that the symptoms entirely absent one moment are suddenly developed the next by some change in posture. Thus Brunton has pointed out that in many cases of heart disease the patient is much benefited by full doses of digitalis, but that it is dangerous for that patient to suddenly stand erect lest he have an attack of cardiac syncope due to the upsetting of the circulatory balance when it is under the influence of digitalis. What the cause of this is we do not know. It is certainly not due to weakness, for the cardiac beats when they occur are in themselves more forcible than in health.

The probable explanation of this peculiar cardiac irregularity lies in a disturbance of the co-ordinating apparatus of the various parts of the heart muscle. By this the author does not refer to the so-called co-ordinating centre of Kronecker and Schmey, which probably does not exist, but to the changes which may take place in the so-called "contraction wave" which begins in the normal heart at the great veins and passes from them through the auricular walls to the walls of the ventricles. It has been found by Wooldridge and by Tigerstadt that if the auricles and ventricles be separated by a ligature or clamp they still continue beating, but no longer do so synchronously; or, in other words, the centres of each set of walls act independently of the others. The irregular action of the heart under digitalis is probably dependent upon this disassociation of its parts, and this theory is still further substantiated by the experiments of Roy and Adami, who have proved that independent contraction of the various parts of the heart can be produced by stimulation of the peripheral end of the cut vagus, a part of the nerve which is stimulated by

digitalis in these large doses which we have been considering. The reason therefore that the cumulative action of digitalis is more noteworthy than that of other drugs is that this effect is more apt to occur and to occur suddenly, and that it does not develop premonitory symptoms which force themselves as warnings upon the physician who is careless in its use or does not know the susceptibility of his patient.

That the symptoms to which the term "cumulative effect" is applied are practically identical seems proved by general consensus of opinion regarding them. Thus Von der Heide agrees with Withering (*An Account of the Foxglove and Some of its Medical Uses*, 1785) that two sets of phenomena take place: first, abnormal cardiac slowing, an irregularity, smallness and rapidity of the pulse after large doses; and second, vertigo, nausea, cramps, and sleeplessness. Husemann speaks of these circulatory and nervous effects, and of the slow, small, and intermittent pulse; and as Edes says, most authors intend by the use of this phrase, "cumulative action," to denote the sudden supervention of toxic symptoms, and in most cases a rapid, or at any rate a feeble and irregular, pulse.

Again, we find in Soullier's *Thérapeutique* (*loc. cit.*), published in Paris in 1895, that the dominant symptoms of digitalism, or that condition resulting from the overuse of this drug, are gastro-intestinal disorders, nausea, and vomiting, cold sweats and general malaise. The pulse is exceedingly slow and filiform, and finally arrhythmical. Sometimes convulsions, dilated pupils, and respiratory oppression are met with, and this condition arises from the retardation of the absorption of the first doses of the drug. Reil states that the symptoms consist in pain in the epigastrium, nausea, great feebleness, amblyopia, and a feeling of weight in the head. Duroricz (*Académie de Médecine*, Mai 27, 1879) mentions the abuse of the alcoholic preparations of digitalis, and after naming a somewhat similar train of symptoms as already given as resulting from overdoses he states that symptoms simulating meningitis may occur. Trousseau has also pointed out that full doses produce hallucinations, delirium, and a slow pulse of 32; and this is endorsed by Peter (*Bull. de Thérap.*, 1883, p. 108). The statements of Duroricz, Trousseau, and Peter refer rather to poisoning than to effects resulting from cumulation, but it is of interest to note that the symptoms are much the same. It is also of interest to note that Raymond Tripier (*Revue de Médecine*, 1883, 1884, 1885) points out

that in some persons digitalis causes a slow pulse, syncope, or epileptiform attacks, cardiac arrhythmia or bigeminal pulse, digestive disturbance, and pains resembling those of rheumatism in the limbs.

It is evident therefore that the circulatory disorders under digitalis are practically identical, whether a poisonous dose be taken at once, or it accumulates slowly and is then all absorbed, which is practically equivalent to one large poisonous dose; or that a person with an idiosyncrasy is poisoned by a dose which would not poison an ordinary individual. Soullier goes so far as to state that in the presence of digitalin we should institute treatment consisting of coffee, or caffeine, and strychnine.

In order that I might obtain a consensus of opinion from those best able to speak of this matter in an authoritative manner, I sent the following series of questions to a large number of eminent practitioners and teachers, and have drawn the following information from their replies:

(These gentlemen were: I. E. Atkinson, M.D., Professor of Therapeutics in the University of Maryland, Baltimore; F. C. Shattuck, M.D., Professor of Clinical Medicine in Harvard University, Boston; H. C. Wood, M.D., Professor of Therapeutics in the University of Pennsylvania, Philadelphia; W. H. Thomson, M.D., Professor of Therapeutics in the University of the City of New York; Abraham Jacobi, M.D., Professor of Diseases of Children in Columbia College, New York; James C. Wilson, M.D., Professor of the Practice of Medicine in Jefferson Medical College of Philadelphia; Edward G. Janeway, M.D., formerly Professor of the Practice of Medicine in Bellevue Hospital Medical College; James Tyson, M.D., Professor of Clinical Medicine in the University of Pennsylvania; James T. Whittaker, Professor of the Practice of Medicine in the Medical College of Ohio; Dr. John H. Musser, Assistant Professor of Clinical Medicine in the University of Pennsylvania; Dr. T. Lauder Brunton, of London; Dr. G. L. Peabody, Professor of Materia Medica and Therapeutics in the Medical Department of Columbia College; Dr. A. D. Blackader, Professor of Materia Medica and Therapeutics in McGill University, Montreal.)

1. Do you believe in the possibility of, or have you met with, the so-called cumulative action of digitalis?

2. If so, under what conditions has it occurred as to disease, dosage,

and age of patient? or, in other words, what do you think predisposes to the development of these effects?

3. If you have met with it, what have been its chief manifestations?

4. What preparation of digitalis is most apt to produce this condition?

5. Has the presence of fever in your experience interfered seriously with the production of the physiological effects of digitalis?

In answer to Question 1—"*Do you believe in the possibility of, or have you met with, the so-called cumulative action of digitalis?*"

Dr. I. E. Atkinson, of Baltimore, states that he believes it possible for digitalis to produce cumulative effects, and he has seen two or three cases which gave very positive evidence of cumulative action.

Dr. Frederick C. Shattuck, of Boston, does not believe that digitalis possesses any more cumulative action than any other powerful drug which is given in full dose, particularly if there be idiosyncrasy present.

Dr. H. C. Wood, of Philadelphia, makes the following characteristic reply: "May I answer your inquiries in regard to the so-called 'cumulative action of digitalis' by saying that those who deny its existence are in a similar position to the famous King of Siam, who banished from the Court in deep disgrace the traveller who told him that he had seen the tops of rivers so solid that one could walk over them?"

A belief in the cumulative effect of digitalis is also recorded by Jacobi, who, when asked for an opinion, referred me to his *Therapeutics of Infancy and Childhood*, in which he says: "When large doses have been given for some time accumulation of the effect takes place."

Dr. William H. Thomson has also met with this condition, and reports a case (see further on).

Dr. J. C. Wilson states that he has "never encountered the cumulative effects of digitalis."

Dr. Janeway replies that he has met with it.

Dr. Tyson states that he has met with it, although he does not believe that the term conveys an idea of the mode of its production.

Dr. Whittaker replies: "I do believe the possibility, and have seen cases, of excessive action; whether it could be called cumulative or not I am not prepared to say from my own experience."

Dr. Musser has "never met with it and does not believe in it."

Dr. Lauder Brunton writes as follows: "I think that digitalis is cumulative; at any rate one certainly finds that after it is used for a while disagreeable symptoms occur. In my own experience these are generally shown first by the stomach in the form of nausea and vomiting. Just the other day I had a case in the hospital where, under the influence of digitalis great improvement occurred at first, then the pulse became more rapid and irregular. Instead of increasing the digitalis, as it was my first impulse to do, I knocked it off entirely and put the patient upon bismuth and soda, as I considered that the cardiac disturbance was the reflex from the stomach, and that the gastric disturbance was due again to digitalis. The result appeared to show the correctness of my ideas, as the patient began to improve forthwith. I almost never give it in fever, so that I cannot answer your fifth question, nor can I say which preparation of digitalis is most apt to cause disturbance. The whole question is an exceedingly complicated one, and I regret I cannot give you more definite answers."

Dr. Peabody has never met with this phenomenon.

Dr. Blackader replies: "Yes, to some extent. Too frequently repeated in large doses, it may accumulate in the system more rapidly than it is eliminated."

In reply to Question 2—"*If so, under what conditions has it occurred as to disease, dosage, and age of patient; or, in other words, what do you think predisposes to the development of these effects?*"

Dr. Atkinson states: "The cases have always been of organic heart-trouble, when the patients have continued to take digitalis upon their own responsibility and for protracted periods—in one case for nearly three months."

Dr. Shattuck states: "I have seen the toxic—cumulative—effects of digitalis under the greatest variety of diseases, dosage, and age. It has seemed to me, speaking broadly, that the greater the real necessity for the drug the less the danger of toxic action, and yet now and then I come across a case, as that mentioned, where a drug similar in its action to that of digitalis agrees while the latter distinctly disagrees. A predisposition to toxic effect depends, as it seems to me, on (*a*) ill-judged exhibition—giving the drug when it is not required—and (*b*) individual peculiarity not to be known beforehand."

Dr. Wood states in his book that it is connected with slow absorption and elimination, and is much more prone to occur when there is no diuretic effect. It is very apt to take place after tapping. Brunton thinks this effect is apt to take place at the development of crisis in fevers.

Dr. Janeway has met with the cumulative effect especially in Bright's disease, and possibly occasionally in pneumonia and in heart disease. He thinks the conditions produced by the continued use of the drug, and that pushing the drug when the heart has become slowed or irregular, soon develop the cumulative effect.

Dr. Tyson says it occurs under circumstances which interfere with a prompt absorption of the drug, or at least its transmission to the centres in which it acts in producing its effects, followed by a sudden removal of such obstacle. Such removal is brought about by brisk purgation, by the removal of accumulations of fluid in the peritoneal or pleural cavities, and especially by a blood-letting practised when such obstacle exists.

Dr. Whittaker says: "The excessive action has resulted from too long administration—that is, from use continued after the effects of the remedy had been obtained."

Dr. Blackader says: "Untoward symptoms are most apt to development when the heart muscle is to any degree diseased."

In answer to Question 3—"*If you have met with it, what have been its chief manifestations? What preparation of digitalis is most apt to produce this condition?*"

Dr. Atkinson says: "The chief symptoms have been profound debility, with a tendency toward syncope, nausea, very slow pulse while in a recumbent posture, becoming rapid and feeble upon exertion. He has no recollection or memoranda of effects upon the vision or kidneys. The urine was not suppressed. Recovery followed within a few days after the drug was abandoned. The dose had not been increased and was not large." His cases used the tincture.

Dr. Shattuck states: "The toxic effects as far as I have seen them —and they have occurred many times under my observation—are anorexia, nausea, vomiting, a weakened and irregular pulse, and diminution in the urine. The toxic effects depend on the purity of the drug rather than the preparation."

Dr. Wood also states (see also answer to Question 1) that sometimes

the first marked symptom of this action is severe syncope, followed by paraplegia, vomiting, diarrhœa, insensibility, and death. Usually, however, only the change in the pulse occurs if the drug is not pushed. "A single case from my own experience will suffice: A woman was taking digitalis freely, with the hope of bringing about absorption of a pleuritic effusion; after many days no effect was manifest from the drug, until suddenly her pulse, which had been running about 90, fell to 75. The use of the digitalis was immediately discontinued. The next day the pulse was 60; the next day 50; the next day 40; with all the characteristics of over-digitalis action. It was nine or ten days before the pulse had regained its normal rate. In conclusion, I see no reason for supposing that one preparation is more apt than another to accumulate."

Dr. W. H. Thomson, of New York, replies as follows: "I can report one unmistakable case of dangerous and specific symptoms of cumulative action of digitalis in a phthisical patient, female, aged twenty-five years, after taking Niemeyer's pill, one three times daily, containing one grain of powdered digitalis, for six days. There was no reason to suspect that the pills themselves had accumulated in the *primæ viæ* previous to the sudden onset of the symptoms, which were deathly nausea and vomiting continuing for eighteen hours, with very intermittent pulse. Every measure failed to stop the vomiting until half a grain of morphine was given subcutaneously, which then arrested it. Patient lived for two years afterward without any similar experience. There was no renal element in this case."

Dr. Jacobi (*loc. cit.*) says the pulse becomes quite slow and irregular and vomiting sets in in this condition.

Dr. Janeway has found the chief manifestations of this state to be sudden death on exertion, and he adds: "I have in the past, on several occasions, made post-mortem examinations of persons who have been under treatment in hospital with digitalis who had dropped dead on going to the water-closet; also in pneumonia under treatment with digitalis some are inclined to hold sudden death due to digitalis. It is somewhat difficult to be certain in these cases."

Dr. Tyson replies almost solely slowing of the pulse, at times to forty or even less beats per minute. He does not think it is peculiar to any form of the drug, though he has met it most frequently when using the tincture.

Dr. Whittaker says: "The chief manifestation was the hard, slow pulse, with subsequent exhaustion of the heart, and paralysis. I have seen the condition only after the use of the infusion, which is usually given in larger dose."

In reply to Question 4—"*Has the presence of fever in your experience interfered seriously with the production of the physiological effects of digitalis?*"

Dr. Atkinson states as follows: "In my experience the presence of fever modifies the action of digitalis very profoundly; in the various febrile conditions in which the heart often shows evidence of failing (typhoid fever, pneumonia, etc.) digitalis is notably inferior to strychnine and alcohol, and indeed, as a rule, fails to influence either the frequency or force of the heart's action or to increase arterial tension. In my experience the febrile condition in great measure prevents the action of digitalis, as shown in the afebrile state."

Dr. Shattuck states: "I have thought that a febrile patient seemed less likely to be upset by digitalis—or evidently so. I may add that if I prescribe digitalis for a patient who cannot communicate with me promptly, and whose condition is not urgent, I am apt to give the drug only twice a day, at twelve-hour intervals. This is with the idea of diminishing the liability of toxic or unpleasant effects of the drug."

Dr. Thomson states: "In my opinion digitalis has no beneficial effect upon the heart when weakened by fever. In diphtheria its effect is most disastrous."

Dr. J. C. Wilson: "The effects of digitalis are not manifested in febrile cases in the same way nor to the same extent as in other conditions. This appeared to me, however, to be due not so much to high temperature as to associated derangements, especially in part malnutrition of the heart muscle."

Dr. Janeway replies that in his experience the presence of fever "does not necessarily" interfere with the effects of digitalis.

Dr. Tyson replies: "I cannot say that I have observed such interference."

Dr. Whittaker says: "It seems to me that the presence of fever, by delaying the absorption of the remedy, interferes with its physiological effects."

Dr. Musser says that he has never secured physiological effect in the presence of fever.

Dr. Peabody thinks that fever does interfere with the effect of digitalis.

Dr. Blackader states that the presence of fever to some extent antagonizes the action of digitalis, and therefore demands a larger dose to produce the same physiological effects.

Reil has remarked upon the fact that cumulation occurs less frequently when digitalin is given than when the infusion is used, because he thinks that digitalin gives warning of its excessive effect, whereas the infusion does not.

It is interesting to note in connection with the answers to the last question, as to influence which the presence of fever exercises upon the action of digitalis, that almost every therapeutist recognizes that fever does prevent digitalis from acting. In my earliest days as a physician in charge of patients in the wards of a large hospital I noted this fact, and on searching for similar experience as recorded in literature I found both such experience and careful pharmacological research pointing to the truth of my observation. Thus, as long ago as 1865, Thomas recorded the fact that digitalis does not act in certain cases of pneumonia, and Brunton Hush then proved that the failure of the drug to slow the pulse depended upon the fact that the inhibitory action of the vagus centres, ordinarily stimulated by digitalis, is lessened by heat, and that the peripheral ends of the vagus are also depressed. A belief that this cause exists for the non-appearance of the physiological action of digitalis is expressed by Wood.

DISCUSSION.

Dr. William Osler: I think that such cases as Dr. Hare has mentioned may occur, but they must be excessively rare. I am in the habit of giving digitalis freely and in large doses, and I have never yet seen what I would call a cumulative action. We all know the slow pulse of digitalis, but I find that all do not recognize that under the influence of the drug we may have the heart beating at the normal rate of about 80 beats a minute and a pulse of 40 at the wrist. The extreme rarity of the cumulative action of digitalis is shown by the fact that it may be taken for year after year in chronic valvular disease without producing any effect. I know a man who took ten minims of digitalis three times a day for three years. While not denying that digi-

talis may have a cumulative action, I think it is so excessively rare that it may be left out of consideration.

DR. E. G. JANEWAY: The question on which I will speak is, Do we always attribute sudden death, even when disease is present, to the right cause? I have had such cases come to autopsy without finding a satisfactory cause of death unless we investigated the medication as well as the disease with which the patient was afflicted. In certain instances where patients, particularly under treatment for Bright's disease, have dropped dead suddenly on going to the water-closet, it was ascertained that for some time these patients had taken large doses of digitalis, as a tablespoonful of the infusion every three to six hours. Now it seems to me that, failing to find a satisfactory explanation of the sudden death as a result of the conditions of disease present, we must ascribe it to the associated medication. I have, moreover, been forced to this conviction by meeting at times patients in hospitals, with slow pulse and slow heart-rate as well, who had been for some time on the doses of digitalis above indicated. I am, moreover, inclined to believe that at times some of the sudden deaths from pneumonia may possibly be from prolonged over-use of digitalis.

DR. GEORGE WILKINS: Like my friend Dr. Osler, I am in the habit of using digitalis; but, unlike his, my experience has been different. I have had several cases in which the cumulative action of digitalis has been well marked. They are generally persons suffering from chronic heart-trouble for years, who have been taking large amounts of digitalis, and probably in very large doses. I will cite one case. This patient, who was suffering from symptoms indicating loss of compensatory power, when œdema made its appearance would take the digitalis at times without consulting me; but always, after taking it for about a week, he would suffer so much from nausea and, at times, vomiting, that he would be obliged to desist, when the unpleasant symptoms would pass away, to return again at about the same interval of time after resorting to the drug. This occurred so repeatedly that there could be no doubt it was due to the large doses of digitalis which he had been taking. A month or two ago he was taking large doses of digitalis, and while sitting up in bed he died suddenly from a syncopal attack which I thought might have been associated with the large doses of digitalis.

DR. J. C. WILSON: It seems to me that the converse of the proposition stated by Dr. Janeway should be considered. Patients who have been taking digitalis or any other drug may die of the disease for which these drugs have been administered. Hospital patients who have been taking digitalis because of chronic valvular disease are not exempt from the dangers of death inherent to the cardiac lesion, and while sudden death in such cases may be due to the digitalis, it is more likely to be due to the disease. If I understand aright the use of the English word "cumulative," I have never

seen such action follow the proper administration of digitalis. I concede that I have seen the toxic influences of digitalis just as I have seen the toxic influences of alcohol, but I have yet to hear a dispassionate discussion of the cumulative effects of alcohol. It is a mere question of dosage and elimination. My use of digitalis is, perhaps, more restricted than that of the reader of the paper. I do not give it in croupous pneumonia as a routine treatment —never except in response to clear therapeutic indications; nor do I give it in the cardiac asthenia of fevers, having long since satisfied myself that this drug is not only useless under such circumstances, but not well borne by the stomach. I do, however, give digitalis in valvular disease of the heart, and in relatively large doses. I frequently administer the tincture in doses as high as 10 or 15 minims three times a day for weeks without witnessing bad effects. Of course, doses larger than can be eliminated produce toxic effects, but these I rarely see; first, because when satisfactory results follow I stop the use of the drug for a time, and under any circumstances I administer it in interrupted courses.

DR. JAMES T. WHITTAKER: I would like to add my testimony to that of those who believe in the cumulative action of digitalis. I believe that if digitalis be given for a sufficiently long time, we will get the cumulative effect of the drug, and I believe I have seen that condition repeatedly. On the other hand, when digitalis is withdrawn and spartein or strophanthus given in place of it, the distressing symptoms disappear. In small doses we are likely to see this cumulative action, but in large doses we seldom see it. If small doses be persisted in—say 10-drop doses—we are very likely to have nausea in the course of time.

DR. CHARLES CARY: I will not detain the Association long, but as a therapeutist I want to say that I have personally never seen any serious poisonous effects from digitalis, though I teach that it is cumulative; the time-limit put upon the use of the drug by authorities is, in my opinion, too short. I have at present a patient who has been taking digitalis or strophanthus for fourteen months, and is now taking five drops of tincture of digitalis and five drops of tincture of strophanthus every three hours, so that she gets six doses a day, and has taken this amount for months. She came under my care for organic cardiac disease, with complications. I have withdrawn 190 pounds of fluid from the abdomen in this case, which may have had some effect in preventing the cumulative action of the drug.

DR. A. MCPHEDRAN asked as to the significance to be attached to the term "cumulative." It was an unfortunate one. Did it mean an accumulation of digitalis in the system, or the exhaustion of the nervous system from overstimulation? On account of its protracted effects it should be given at long intervals; the frequent administration of small doses at short intervals was irrational.

DR. H. A. HARE, in closing the discussion, said: I simply want to say that Dr. Osler has proved just what he tried to disprove. If that is not getting the cumulative action of digitalis when you have a pulse of 40 at the wrist and of 80 at the heart, I do not know what to call it. When I say that the drug has a cumulative action I do not mean to say that it accumulates in actual quantity in the system; I mean that it affects the heart more and more until it is overstimulated. I should have read the abstracts in my paper from the directions of foreign therapeutists to give digitalis in large doses and at long intervals, and then to remit its administration. Even after several days' interval you will still be getting the effect of the previous administration.

I have studied a number of therapeutical preparations of digitalis, and I find that not only do they contain a different proportion of the active principles, but that the digitalis leaves from different parts of the world vary in strength. Taking samples of tincture of digitalis prepared in different cities, it will be found that the samples manufactured, say in Buffalo, differ from those made in New York, one containing more digitonin and less digitalin, and another more digitalin and less digitonin. Again, some of these active principles are soluble in water and others in alcohol, and therefore we get different effects from the use of the tincture than from the use of the infusion. In conclusion, let me say that out of the twelve or fifteen letters of inquiry I sent out asking about the cumulative action of digitalis only two replied that they did not believe there was any such thing in existence.

DR. F. H. WILLIAMS: I would simply like to speak of a rule I follow in the administration of digitalis. In my service at the Boston City Hospital I always have a record kept of the twenty-four hours' urine, as well as a record of the pulse. If the amount of twenty-four hours' urine, after it has been increased by the digitalis, suddenly diminishes, or if the pulse is slowed, I suspend the administration of the drug. If the patient is kept in bed and these precautions are followed, I think it is safe to give digitalis until one of the above-mentioned symptoms appears.

THE RELATION OF NEURASTHENIC CONDITIONS TO THE GENERAL NUTRITION, WITH REFERENCE TO (A) BODY-WEIGHT; (B) BLOOD MEASUREMENTS; (C) EXCRETION OF UREA, URIC ACID, INDICAN.

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(A) The opportunity offered by having under observation, for periods often covering several months, a considerable number of patients with symptoms chiefly of the depressive type, and, for the most part, not connected with known organic disease, has induced me to compare their progress with certain theories, or, perhaps, I should rather say feelings or assumptions, not always definitely stated, but as it were in the air; to the general effect that these symptoms are largely or wholly dependent on insufficient or unsuitable nutrition, as displayed either by a certain amount of emaciation or anæmia, or upon autogenetic toxic influences.

These impressions have in their support the highly important fact that no plan of treatment which affords a prospect of anything like enduring success can afford to leave them wholly out of sight. So far as body-weight, which, of course, depends on the harmonious working of more than one function, is concerned, by far the greater number of my cases seem to fully confirm the popular view. In the great majority a steady gain in body-weight went hand-in-hand with improvement in nervous symptoms; sleep was better, general depression and nervous restlessness and local pain were less, and the brain increased its capacity for normal action without exhaustion. Little need be said about these. The results are what we expect, and fortunately usually find.

Some special groups, however, may be selected which are partly

confirmatory and partly incompatible with these ideas, which go to show that although the two processes of improved general nutrition and returning nervous strength do go so nearly hand-in-hand, they are not one and the same, and it is not always easy to say which leads. The first group consists of a certain number of cases, fortunately not large in proportion, which confirm the rule upon the other side, and go to show that a persistent refusal to take on flesh, notwithstanding rest and careful feeding, with their adjuncts, is of decidedly unfavorable prognosis as regards speedy recovery, even when no other organic change can be discovered.

Miss D., aged twenty-two years, tall, with a delicate, rosy complexion, lost weight from 148 to 125 pounds during eleven months, interrupted during one month by a slight gain. She had persistent backache and headache, and frequent gastric disturbance. Since leaving the asylum she has had several severe turns of gastric disturbance originating at the time of menstruation, but much outlasting it. Menstrual pain and backache have been somewhat better since the uterus was curetted, and her family recognize a decided improvement in the two years that have elapsed since her discharge.

Miss D., aged thirty-eight years; had tumors, supposed to be malignant, but after removal found tubercular, removed from one breast and axilla. A year later she entered the asylum, chiefly on account of general weakness and headache. She was of a singularly cheerful and hopeful disposition, but lost weight steadily, though slowly, from 113 to 104 pounds. There have been enlarged glands upon the other side, but no manifestation of tuberculosis elsewhere, and she remains an invalid.

Miss F., aged twenty-eight years, a chronic, probably congenital, neurasthenic, with choreic movements, much aggravated by any mental disturbance; lost weight from 103 to 83 pounds in a year. She is now supposed to be slowly improving.

Miss B., aged twenty-five years, lost seven pounds in nine months, and got back five of them in the next four. She improved greatly after a considerable time, partly under the auspices of a faith cure.

Miss H., aged forty-five years. Alternations of gain and loss for seven months, with maximum variation of five pounds, and final loss of a pound and a half. Had severe neuralgic pains, chiefly sciatic. A short time after leaving the asylum she was sent to an insane hospital, but is now comparatively well.

Miss C, aged thirty-three years. Had ups and downs of weight for nine months, at the end of which time she was half a pound lighter than when she began. She improved very slowly, and has continued to do so, but still is not strong, and does not sleep well.

Miss M., aged twenty-seven years. Weight fluctuated for six months, ending with a total gain of half a pound. She is better, but not well.

Mrs. H. After a stay, during which she was greatly improved, but unfortunately for my present purpose not weighed, was with us again for six months, during which her weight varied from 119½ to 122 pounds, but began and ended at 120. She developed distinct mental symptoms, and died some months later in an insane hospital.

Miss B., aged thirty-eight years. Lost five pounds in four months. Her disposition was of the reticent, worrying, and morose kind, which is not likely to be radically changed, and which continues to vary in its manifestations rather in accordance with the pressure of her responsibilities than with the state of her nutrition.

Miss G., aged thirty years. Gained a pound or two in nine months, then lost six and gained four. There was no very decided improvement, but I have been unable to hear from her since.

Mrs. D., a large, flabby, pale woman, exhausted by a large family; had ups and downs of weight for nine months, with a final loss of three pounds. She is in essentially the same condition.

Miss T., aged thirty-seven years. Tall and thin with a complexion of almost doughy whiteness and low blood color; has had a headache so persistent that the suspicion of an intracranial growth has been often entertained but never justified. The question of interstitial nephritis might easily be raised, but seems to be answered in the negative by the table near the end of this paper. She has at times, but not constantly, gastric disturbance. She lost six pounds between July and August, which she made up again by November (during the gaining season), but since that time has steadily lost again, and is nine and one-quarter pounds lighter than when she entered. Her prospects of recovery at best seem very remote, although just now she seems to be gaining a little strength.

A catalogue of cases in which gain in weight took place, with very decided but only temporary improvement, would prove nothing but the too obvious fact that a fair degree of bodily and mental comfort may be maintained in the shelter of a hospital, which cannot be continued after the patient has been again brought in contact with the labors and trials of everyday life.

In some cases the apparent improvement in nervous strength lags so far behind that in weight, that the connection between them, even if real, is not very obvious. Mere timidity or lack of confidence resulting from too long a disuse of the powers actually present may restrain the patient from tests to which she responds well enough when the attempt is made with determination. If a faith cure intervene at this stage, the bodily condition which makes it possible is very likely to be overlooked in wonder at the miracle.

The following cases, however, were instances of a discrepancy more

decided than mere delay between the bodily and the mentally improved condition.

Miss E., aged fifty-two years, was the more than faithful and overzealous head nurse at a hospital. She experienced some sudden cerebral sensation, not attended with paralysis, from which she dated her illness. She gained ten pounds in four months, and improved greatly in bodily appearance, but remained in a condition of more hopeless despair without a trace of a delusion than is often seen outside the limits of melancholic insanity. Nearly two years later there had been no change for the better.

Mrs. S., aged thirty-four years, has gained twenty pounds in eight months, and has an excellent blood color, but she sleeps hardly better than when she entered, and complains constantly of distressing thoracic sensations for which no anatomical basis can be found.

Miss R., aged thirty-one years; reticent and suspicious; had gained from 104 to 111 pounds when her suspiciousness was noted as on the increase and becoming more definite, A few days later it was noted that her delusions were increasing, and she was discharged to the McLean Hospital.

Many other cases might be added, somewhat less striking, but going to show that the proportion of potential energy obtained by the nervous centres from a given amount of fat and blood may vary from almost nothing, as in the three instances just given, up to the normal, as seen in the great majority.

A second group is composed of the cases where the gain in nervous strength takes place without any important gain in weight, and is, when represented by what might be called acute cases, naturally enough not a large one in hospital practice.

It is, however, amply supplemented by the very large number of such cases observed in everyday life, where normal and even excessive nervous and intellectual function is carried on with a degree of general nutrition below the average—cases which come under medical observation only incidentally or manifest such rapid recuperative powers that they do not become invalids at all.

The hospital physician does not so frequently have the pleasure of seeing them recover, because they do not remain sick long enough to come under his care, and because, also, when they are submitted to a treatment directed toward this object, they, too, can take on flesh, and thus seem to be specially good examples of the rule, while in reality this gain is only an accidental adjunct and in no way essential to recovery.

An easily recognizable subdivision of this group is found in the cases of normal weight or perhaps even a little overweight, when a change of habits of life or of treatment may reduce it somewhat.

An interesting instance of this occurred in Miss P., who gained six pounds in weight, but nothing in symptoms, during the four months in which she was treated for simple anæmia and debility; but when her case was recognized somewhat tardily as one of myxœdema, and treated by thyroid, lost ten and a half pounds, with recovery. She was twenty-four years old, the youngest case I have ever seen of this affection.

A few cases of a more chronic character illustrate further the fact that the interdependence of the two sets of phenomena is not absolute, and, on the other hand, the great desirability of a somatic basis to insure the success and permanency of psychic therapeutics.

Miss C., aged twenty-eight years, brunette. Lost two pounds in seven months, from 98 to 96 pounds, having in the interval gone for one month above 100 pounds. Her improvement in strength was steady, and has continued.

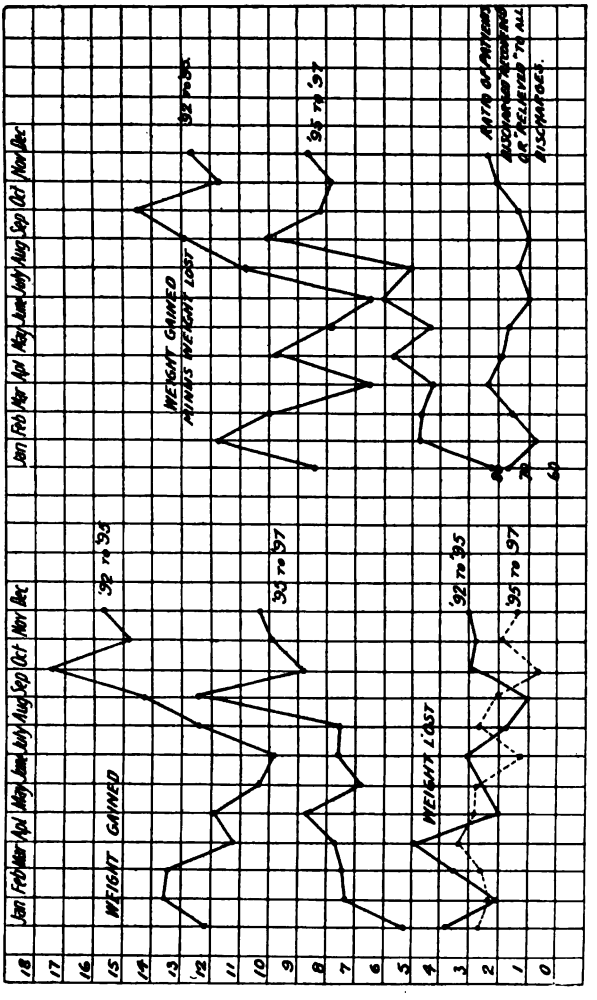
Miss H., aged twenty-six years, with a complete paraplegia, undoubtedly of hysterical character, and obstinate resulting contracture, had not walked for eight years. She was not weighed for many months, but certainly did not gain greatly in flesh. She then lost steadily, from 91 to 87 pounds. After long-continued massage, passive motion, and so on, she began to walk, and when discharged could traverse the length of a long entry unassisted. Soon after her return to her home she was alarmed by a fire, and relapsed, just how completely I do not know. She has made a second recovery under some form of faith-cure, which might easily have been more speedy than the first, as the contracture and the eight years' inertia no longer had to be overcome.

Miss M., aged about thirty-five years, increased from 132 to 160 pounds in five months, and then gradually fell off to 150 pounds without interruption in the progress of improvement.

An interesting incidental fact noticed while looking over the weight records has been put in the form of curves based upon three years' and two years' observations—*i. e.*, that the general gain in weight is considerably more in the later summer and early autumn than during the winter and spring. This has been before remarked of the growth of children.

I have placed underneath, as a matter of curiosity, a line representing the ratio of cases "discharged," "recovered," or "relieved," to

all discharges, for five years. This is, of course, extremely vague, but might, perhaps, be interpreted to show a certain amount of correspondence between improvement in nervous symptoms and gain in


WEIGHT GAINED
WEIGHT LOST
'92 to '93
'93 to '94
'94 to '95
'95 to '96
'96 to '97
Jan Feb Mar Apr May June July Aug Sep Oct Nov Dec
18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0

From weighings of patients February, 1892, to February 1896; February, 1895, to March, 1897.

weight, the latter showing its effect after a month or two. The fall and rise in the early part of the year may depend upon the seasonal effect in preventing changes during the severe weather, and a consequent removal to the country as the warmer months approach.

(B) In speaking of the correspondence of nervous symptoms with anæmia it is very necessary to take into account the ambiguity of the word, which is used on the one hand to mean a diminished blood-supply, and on the other a proportion of corpuscles, or hæmoglobin, or of both, diminished below a more or less arbitrary standard, or below the average. When a local anæmia is spoken of it is usually the former—*i. e.*, a deficient supply that is intended, for although it has long been known that the chemical composition of the blood varies within different portions of the arterial circulation, and recently the counts of J. K. Mitchell have shown that the corpuscles also cannot be distributed with absolute uniformity, it has not been usual to take cognizance of these facts in clinical language. The greater or less amount of blood in a given region can sometimes be estimated with some approach to accuracy, but it cannot be expressed in figures.

On the other hand, anæmia, as a name of a disease or symptom without any anatomical limitation, is generally taken to refer to the latter condition—*i. e.*, deficiency of the blood in corpuscles or color which can be measured with a degree of accuracy not at all commensurate with the apparent delicacy of the readings, but still sufficient to be of some value.

The total amount of blood in a given body is quite impossible to measure without withdrawing a quantity inadmissible in modern therapeutics, and it can only be roughly estimated by comparison of complexion, color of mucous membranes, and blood pressure, with measurements of hæmoglobin or corpuscles. Facial complexion is especially fallacious as a measure of the amount of hæmoglobin, and is much more dependent upon a proper degree of general and local vascular tension and cardiac vigor as well as upon individual differences in the capillary supply of the skin. The mucous membranes, especially the conjunctivæ, bring us somewhat nearer to roughly correct estimate on the latter points.

So far as I have seen, an estimate of anæmia based upon the general look of a patient is quite as likely to coincide with the severity of nervous symptoms as the measurements of the hæmometer, but it is much less easy to put in figures.

I am fully aware of the considerable limits of error in the latter instrument, even when used with great care, and, I think, I have ven-

tured on no deductions drawn from small differences of individual readings.

The following table gives the blood measurements of a number of patients and employés, mostly females, divided in groups corresponding to each five degrees of Fleischl:

	Female patients.	Female employés.	Male patients.	Male employés.	
1 . .	1	...	1	...	100 or more.
2 . .	4	1	2	...	95 to 100
2 . .	3	1	...	...	90 " 95
3 . .	10	2	1	1	85 " 90
3 . .	14	6	...	1	80 " 85
4 . .	29	8	1	1	75 " 80
4 . .	22	5	...	2	70 " 75
5 . .	15	7	...	...	65 " 70
5 . .	5	0	...	...	60 " 65
6 . .	7	1	...	...	55 " 60
6 . .	2	0	...	...	50 " 55
7 . .	3	1	...	...	45 " 50
7 . .	0	0	...	...	40 " 45
8 . .	4*	1*	...	...	Below 40

39, 35.
* below 15. * 25

The greatest number of cases among the patients are placed between 70 and 80 and the greatest number among employés no higher, so that it is fair to consider 75 as a normal, measured by the Fleischl, among women who are not invalids, but are not exceptionally robust.

It is impossible to draw any line which would distinctly separate the severe from the mild cases, but on going carefully over the list I am unable to detect any distinct correspondence of severity of symptoms with poverty of hæmoglobin.

On the contrary, it is easy to pick out from the higher classes several cases distinguished by especial severity and persistence of functional nervous disturbance, and among the very lowest the reverse.

Of five persons with a count below 40, two patients had menorrhagia from fibroids and suffered from some secondary symptoms, one of them from neuralgia, but were by no means of the nervous invalid type. Another was a hypochondriac, but of a cheerful type, if such a description be allowable. One patient with pernicious anæmia, having

color less than 15, a count of less than a million, with extreme poikilocytosis, was indeed extremely nervous; but a laundress with color 25, a count of 700,000 and a complexion to correspond, hardly considered herself sick, and was entirely free from any nervous symptoms. A laundress with 55 and a table girl with 45 are attending to their work.

A small woman (Mrs. H.) with a pale and worn countenance, who was never weighed, because she was supposed to be too weak to be put upon the scales, used to pour forth the longest and most voluble complaints of universal pains to which I ever listened, with complicated descriptions of paræsthesiæ, nervous vomiting and sleeplessness, had a color of 75 and a count of 4,650,000. She was discharged not relieved.

Another pale woman (Miss H.) with successive color-tests, at intervals of a little over a month, of 63, 61, 62, and 75, failed to gain weight, but was discharged relieved. She soon afterward became worse, and later insane, with final recovery.

Other similar cases might be found, but I will mention only three:

Mrs. M. has a somewhat sodden complexion, is weak, low-spirited, and subject to gastric disturbance. Her blood color, several times verified, is 86, which certainly seems to call for a more rapid recovery than she is making.

Mrs. S. has a complexion not pale, but grayish and without any flush. She has gained 20 pounds in weight, and her blood, which has been examined several times on account of the curious want of agreement with her appearance, always gives a color above 80. Her troublesome, but not absolutely constant, insomnia is not materially improved nor the pain, without discoverable basis, from which she constantly suffers.

Miss S. was sent in as a well-marked case of traumatic neurosis. She is distinctly of the hypochondriacal type. Her (legal) case has been settled. Her complexion would be described as pallid, or, perhaps, even doughy, but her blood counts, although the estimates have varied somewhat, have usually been found over 80. She is, however, losing instead of gaining flesh, and there is no decided improvement in her symptoms.

The nerve-centres have a nutrition of their own and receive, according to their own requirements, a larger or smaller share of the nutriment offered by the general circulation. Of course, it cannot be perfect unless a sufficient amount of appropriate nutriment be carried to them by the blood; but it is evident from the state of the blood in many persons with efficiently working nervous systems that quite a wide limit is permissible in the concentration of the fluid which bears it—*i. e.*, that the nervous substance can select and utilize from a solu-

tion bearing the appropriate pabulum in quite widely varying degrees of dilution enough to carry on its ordinary functions without exhaustion. I am not sure, though this is not easy to demonstrate by figures, that this does not apply equally well to the ability to store a reserve force for extraordinary demands.

The rapidity of the circulation, as influenced by cardiac vigor and vascular tension, may be able to compensate for deficiency in composition, since the same amount of blood, if it contains a little smaller percentage of oxygen and peptone, may, by making the circuit more rapidly, convey the same amount in a given time as a richer fluid in more sluggish motion.

On the other hand, a nerve-centre which is incapacitated from selecting and assimilating its appropriate pabulum cannot be forced to do so. We can force food into the stomach and thereby usually fat under the skin, and to a certain extent hæmoglobin into the blood, but it is by no means easy to force potential energy into the neuron and the muscle-fibre unless there exists on the other side a harmoniously acting receptivity.

The restitution of the normal structure of the exhausted neuron is a process of growth, demanding time, rest, and also that unknown element which makes all growth to a great extent qualitatively independent of its surroundings, and not a mere process of osmosis dependent upon a balance of pressures or relative concentration of salt.

When we get beyond mere exhaustion and have to deal not with a temporary deficiency of force, but with acquired abnormalities in its manifestation, or further, still, with congenital peculiarities varying in each case from the mild hypochondriasis of the chronic invalid to the fixed idea of the delusional insane or the paranoiac, the therapeutic value of nutrition alone decreases in proportional importance, although, of course, it is still the basis upon which other and more specific treatment must rest.

Cultivation in plants and education in animals can in a single generation increase the usual output up to a certain limit; and in many generations, and aided by selection, can greatly improve the quality of the product; but no amount of fertilizer can make the stunted pine of the pasture, gnawed and trampled on by cattle and hacked by boys, grow into the stately column of the forest, or the cabbage to secrete cinchona alkaloids or exhale the perfume of the rose.

No amount of oats will make the draught-horse into a racer, and neither beefsteak nor "nerve foods" will make the chronic neurasthenic capable of easy and efficient work. What removal of special obstacles and the adjustment of the work to be done to the best nutrition possible in each individual case, may do in securing the maximum efficiency and comfort in productive labor of the nervous system is another matter.

If there were any way of measuring the potential energy of the neuron, and especially its storage capacity, without exhausting it, we could then get at directly and accurately what we now try to do by inference, and could study the phenomena of fatigue side by side with the means of repairing it.

But trying the experiment of exhaustion, however interesting it might be and instructive as regards theory, would be therapeutically hazardous as regards the individual patient—emptying the reservoir we are trying slowly and laboriously to fill in order to find out exactly how much it holds.

A study of this class of cases in the psychological laboratory, and especially by the continuous methods of Kräpelin and his school, could hardly fail to give results not only of interest but of great value, but would require to be made with great care. I have found in a very few instances that the effort of attention necessary to a trial of simple reaction-time may be felt as a serious strain, and I think that many of us would recoil from frequently repeating such an experiment as trying to commit to memory in the shortest possible time a set of nonsense syllables while some one was reading an interesting book within hearing.

(c) Many papers have been written about the nervous symptoms of lithæmia or uric acid in the blood, and indeed this condition figures among the many comprehensive theories of neurasthenia. But the literature is out of all proportion to the amount of proof that any relation of causation exists between them, or even that uric acid exists in excess at all in the blood in cases marked by neurasthenic symptoms. This acid was found by Garrod many years ago, in cases of gout, by an approximate method, but exact quantitative methods for its measurement in the blood are fitted only for laboratory and not for ordinary clinical work, demanding quantities of blood not afforded by modern

therapeutics. These methods have found it in cases other than gout, as in several forms of anæmia, leucocythæmia, as well as in some diseases causing dyspnœa. Neither of them, so far as I am aware, has detected it in neurasthenia. The whole doctrine indeed rests on plenty of testimony but very little evidence.

A quantity of uric acid varying in either direction from an average or assumed normal, either in twenty-four hours' amount, or in proportion to urea, can of course be readily demonstrated in these as in other cases; but it has been chiefly since the laborious observations and ingenious speculations of Haig that attention has been strongly directed toward uric acid as the special poison causing many nervous symptoms. Before him it did not have even the indirect support of quantitative urinary analysis, but rested merely upon the presence, in connection with certain symptoms, of an increased deposit of urates, a phenomenon which, as is well known, depends upon many other conditions than an increased amount in the circulation, or even an increased elimination. Hence the principal objection to the word "lithæmia" as a name for a group of symptoms of a more or less neurotic character, probably of dyspeptic origin, is that it assumes a definiteness of knowledge which does not exist. If, as seems highly probable, these symptoms are really of toxic origin, it is by no means proved that uric acid is the only or even the usual poison.

Whether this poison is to be found within the uric acid group, as supposed by Rachford, or whether it is a single or more probably a group of products of intestinal decomposition further examinations must show. The tenacity with which the urinary coloring matters cling to uric acid through all the vicissitudes of chemical manipulations may suggest that here, perhaps, may be some explanation of the bad repute of the latter, and that the apparent accessory may be the real principal.

The recent theories of Haig, based upon a large number of careful observations, have been woven into a doctrine so complicated and involving so many suppositions which cannot be either proved or disproved, that it is almost impossible to criticise them fairly without going exactly over his ground and taking continuous observations every few hours for many days.

His fundamental assumption that the rate of formation of uric acid to urea is a nearly constant one of one to thirty-three, I have found very

little to confirm, though I have not followed any one person long enough to justify me in claiming to have established the habit and rate of a lifetime.

Among about one hundred persons examined once or more, I have found this ratio, or very near it, in nineteen persons, and in somewhat more than two hundred examinations about thirty-three or thirty-four times. More than or equalling one in fifty-five, the proportion suggested by Herter as more usual, I have found about one hundred and fifteen times in forty-four persons, including the above.

In going over the records of these cases in the endeavor to find some correspondence approaching constancy between either an excess or diminution of uric acid secretion, and the severity of the other nervous symptoms, or of any special symptoms, the result is far from satisfactory, and this is true both as to the twenty-four hours' output and the proportion to urea.

The nearest to such a correspondence is to be found in some cases of severe headache, where, by assuming as a normal maximum the fraction one-fiftieth, there appears to be an excess of uric acid excreted. But the number of such cases is not large, and with them are others where this proportion is to be found without the headache, and on the other hand the headache occurs with a proportion of uric acid considerably below this, so that it is forcing matters very much to assume a relation of causation in the remainder. It is, of course, true that in order to controvert the views of Haig his method should have been strictly followed and examinations made at more frequent intervals than was done in any case.

Hence there is nothing in these observations to disprove the possibility of a paroxysmal uric acid headache, but they certainly seem to show that a constant neurasthenic headache is not of this character.

Miss P., in nine times out of ten examinations, had a proportion of uric acid in excess of one-fifty-fifth, and twice of one-thirtieth or more. The quantity of urine and of urea was about normal, and the uric acid usually above gm. 500. She complained of constant headache, but her general appearance, her gain in weight, and her subsequent history lead me to doubt very much the severity, if not the existence, of extreme suffering.

Miss D., with a quantity usually below c.c. 1500, and urea below gm. 20, had a proportion of uric acid more than one-forty-fifth, five times in five observations. She has already been mentioned as having constantly lost weight, and being now in a condition of very slow and tedious recovery.

Date.	Quantity.	Sp. gr.	Urea total.	Uric acid total.	Proportion.	Indican.	
Miss G.							
Aug. 16	500	.....	14.0	No app. incr.	.....	Excess	Rather thin and pale, but gained flesh.
Dec. 22	725	1027	20.0	0.810	1/64	No exc.	Headache not noted.
Jan. 18	700	1025	13.6	0.374	1/86	.....	Headache not noted.
Mar. 16	350	.....	16.0	0.213	1/75	Excess	Severe headache, 16 hours.
Mar. 19	600	1080	15.0	0.417	1/36	.....	Headache less severe, 16 hrs.
No. I. No. II.	450	1031	12.2?	0.227	1/53	No exc.	No headache, 16 hours.
Miss S.							
Dec. 31	950	1023	20.0	.....	.....	.....	Stout, florid.
Jan. 1	850+	1024	24.0	0.827	1/72	Increase?	Headache nearly all the month.
" 2	1100	.....	28.5	0.638	1/44	Increase?	Headache.
" 5	1200+	1021	23.4	0.282	1/82	Not incr.	Very nervous.
" 6	1650	1020	30.0	0.569	1/53	Not incr.	Very nervous.
" 7	1600	1020	31.0	0.224	1/139	Not incr.	Very nervous; headache nearly all the month.
Feb. 28	1350						
Mar. 1	1600	1020	23.5	0.288	1/81	Not incr.	Headache.
" 2	1650	1019	.....	.....	.....	.....	Headache.
April 15	1500	1017	21.5	0.217	1/90	.....	Headache for three days.
Miss T.							
Jan. 1	1125	1018	.....	.....	.....	.....	Headache nearly constant for months.
" 4	1650	1017	?	0.775	1	Not incr.	Salicylate of sodium,
" 6	1250	1013	17.5	0.456	1/36	Not incr.	
" 7	1450	1015	19.25	0.602	1/33	Not incr.	
" 8	.....	.....	.....	.....	.....	.....	Stop salicylate.
" 18	1250	1011	11.25	0.131	1/44	Not incr.	
" 27	.....	.....	.....	.....	.....	.....	Severe headache yesterday P.M., vomited.
" 28	.....	.....	.....	.....	.....	.....	Vomited.
" 29	2050	1015	20.5	0.250	1/40		
" 30	2150	1010					
Feb. 1	2050	1008	.....	.....	.....	.....	Headache.
" 5	1300	1020	28.8	0.669	1/46	Decrease?	
" 6	1450	1011	18.0	0.450	1/40	Not incr.	
" 7	1200	1012	16.8	0.474	1/34	Not incr.	
" 8	.....	.....	.....	.....	.....	.....	Head better.
" 14	800	1012	8.20	0.188	1/43	Not incr.	
" 14	Spec'n	1029	.....	.....	1/37	Much increase	
" 15	1200	1012	15.6	0.270	1/57		
" 15	Spec'n	1007	.....	.....	1/8	Not incr.	
" 16	.....	.....	.....	.....	.....	.....	Head better; slept better.
May 2	Spec'n	1022	.....	.....	.....	.....	Urine was examined several times for albumin, and on one occasion a slight trace was found. No casts.

Miss C. used to have attacks of severe hemicrania, beginning with zigzags before one eye, succeeded by headache on the opposite side. She gained weight and improved. Toward the end of her stay she lost weight a little, but continued to improve, and a year or two later called to see me and said she had been constantly better. During the time that she was losing a part of the weight that she gained the observation on page 139 was made.

Two others follow in which the excretion of uric acid does not have any special relation to the symptoms. In one of these (Miss T.) the remarks taken from the record do not correctly express the constancy of the headache, which was practically continuous, hardly intermitting for more than an hour or two at once. It might seem that here, with a constant proportion of the acid beyond what has been found more nearly the usual with us than Dr. Haig's one-thirty-third—*i. e.*, one-fiftieth, or thereabout—we have a strong case in favor of his theory as modified to suit our conditions. In reality, however, it is hardly so at all. Although these observations were made chiefly within two months, the time during which the patient was under treatment, never able to take a full meat-diet, and having not infrequent gastric attacks, having taken eliminatives, with a fair elimination of water all the time, and a quantity of urea quite as large as could be expected with her moderate diet, was much longer. Her headache has been relieved neither by acids nor alkalies. The continuance of the headache up to the present time, then, if caused by a constant flow of uric acid, would argue a previous accumulation of great magnitude.

The existence of such a fund, although it cannot be absolutely disproved, is certainly in the highest degree improbable. There were no indications other than have been mentioned of a gouty diathesis, and in a tall, thin, pale woman with a blood-color of below fifty, losing weight, whose previous history was that of a country school-mistress, supporting herself and a drunken father, we certainly have conditions as little favorable for acquiring lithæmia as can well be imagined.

Dr. Haig's theories are provided with so many ingenious adjustments that it is almost useless to deny their applicability to any case when the attempt is made by willing hands. The assumption of a reserve of unknown quantities of uric acid accumulated under the most adverse circumstances and stored where it is inaccessible to chemistry and betrays itself by no symptoms, places the advocates of the theory in a position practically unassailable.

In a paper by Dr. Gertrude Van Pelt[1] there are a number of cases reported with nervous symptoms supposed to be connected with uric acid. In one of these a chronic invalid, "who had been all over the world in search of health and had all kinds of treatment," the nervous symptoms included neuralgia, headache, insomnia, and dysmenorrhœa. Her urine was always very scanty and often loaded with urates. Now, if such symptoms as these are due to uric acid in the circulation, it seems as if this patient must have been getting rid of it for many years instead of accumulating it, for Haig takes the quantity in the urine as an index of the quantity in the blood. It is not a very far-fetched supposition, either, that such a patient had drunk no inconsiderable amounts of alkaline mineral waters in her day, which could hardly have allowed the process of accumulation to date back to childhood.

It thus becomes very interesting to know how, after taking salicylate of sodium for two and a half months, she could have had a total twenty-four-hours' amount of uric acid very considerably in excess of the normal, and a proportion to urea even more so. The exact figures were nine hundred milligrams and one-eleventh.

The former of these is larger than the average for strong and healthy persons on a full diet; more than I found in my own case with two exceptions; more than given by Luff[2] among fifty determinations in a healthy man on a mixed diet, more than I have ever found in about a hundred persons, many of whom had symptoms not unlike the case described, and very much more than all but a comparatively small number.

The last observation consists in an experiment upon myself to determine whether the passage of uric acid through my circulation would produce a headache.

It will be seen at once that in this point of view it was a failure, since the acid, either solid in the stomach or in the form of urate of potassium in the rectum, must have failed of absorption. It is introduced, however, for purposes of comparison, and with the remark that neither on the days when the total was less than usual (22d) or high (14th and 23d), or when the proportion was at its lowest (22d) or highest (14th, 20th, and 21st), or on any other day was there a headache.

[1] Boston Medical and Surgical Journal, vol. cxxxiv. p. 129.
[2] London Lancet, 1897, p. 947.

Date.	Quantity.	Sp. gr.	Urea total.	Uric acid total.	Proportion.	Indican.	
Oct. 25	.....	.....	.....	.....	1/43		
April 13	1177	.....	36	.....	.....	Increase.	
" 14	1324	.....	.....	0.688	1/53		
" 15	1340	.....	27	0.777	1/39		
Mar. 21	.....	1030	.....	.....	.....	.....	Urea per litre 0.23.
April 11	1200	1026	30	0.768	1/38	Increase.	
" 12	1000	1027	27	0.755	1/36	Increase.	
" 13	1060	1027	33	0.826	1/30	Increase.	
" 14	1300	1026	31	1.007	1/31	Increase.	Sediment of uric acid crystals; evening, took 0.220 uric acid in capsule.
" 15	1280	1030	30	0.787	1/38	Increase.	
" 16	1000	.....	30.3	0.605	1/50	Increase.	Evening took 0.500 uric acid in capsule.
" 17	1050	1028	28.3	0.766	1/37	Increase.	No sediment of uric acid.
" 18	940	1029	35	0.714	1/49	Increase.	
" 19	1300	1027	29	0.760	1/38	Normal or incr.	
" 20	1200	1025	27	0.732	1/30	Normal or incr.	Albumin trace?
" 21	1250	1026	26	0.669	1/32	Increase.	
" 22	1020	.....	27.8	0.527	1/52	Increase.	Club dinner with some wine.
" 23	1340	1027	36.2	0.904	1/40	Increase.	Evening, took 0.500 uric acid, dissolved in KHO, by enema.
" 24	610 620	1027 1027	15.8 16.7	0.399 0.347	1/40 1/48	Increase.	
" 25	1150	1023	27	0.667	1/40	.....	Evening, took gm. 1 uric acid dissolved in KHO, by enema.
" 26	1175	1029	25.4	0.564	1/45		
" 27	1375	1025	32.7	0.701	1/46		
" 28	.....	.....	.....	.....	.....		
" 29	.....	.....	.....	.....	.....	.....	Moderate headache of few hours' duration.

The neurasthenic condition is quite as likely to be connected with an amount of uric acid elimination below the average as up to it, and much more so than with an excess. This, however, is connected not with any storage or special condition of this substance, but is simply a part of a general sluggishness or inhibition of metamorphosis, as shown by diminution in the total amount of urine and of urea. The phosphates have not been examined often enough to give any important indication, and the same must be said with reference to indican considered as an indicator of intestinal putrefaction.

DISCUSSION.

DR. JAMES J. PUTNAM: I do not like to allow such an interesting paper to go by without saying a word about it. I can corroborate the statement of Dr. Edes that neurasthenic patients may look very pale indeed, and yet have a normal blood count and a normal amount of hæmoglobin. It seems as if the conditions under which the blood circulates must have a good deal to do with the symptoms.

The influence of uric acid on the neurasthenic condition is very far from being settled in my mind after reading Haig's work. His writings, attractive as they are, are devoid of the critical spirit needed for dealing with so complex a subject. Metabolism is closely connected with functional nervous diseases, but the part played by changes in metabolism in causing nervous disturbances is in doubt; and still more is it in doubt whether we can give a name to the substances which cause them. In the case of epilepsy, for example, there is room for much doubt whether the changes in metabolism which are found are the cause of the epileptic attacks or the result of them, and it is quite possible that the relationship between them is one of correlation rather than of cause and effect. .

FURTHER STUDIES UPON THE PATHOGENIC SPIRILLA OF THE SCHUYLKILL RIVER AT PHILADELPHIA.

By A. C. ABBOTT, M.D.,

AND

D. H. BERGEY, M.D.

(*From the Laboratory of Hygiene, University of Pennsylvania.*)

In a paper presented by one of us (A. C. A.) at the last meeting of this Association[1] attention was called to the fact that in the water of at least one American river, viz., the Schuylkill, at Philadelphia, pathogenic spirilla had been detected that possess the majority of the characteristics common to that group of spirilla whose most important member is the spirillum of Asiatic cholera. In the course of the discussion that followed several pertinent questions arose, referring notably to the constancy with which this variety was to be detected, its distribution in the river, and to the possibility of its detection in water from other sources. Since the last meeting a part of the time at our disposal has been utilized in answering these questions. It is our intention to embody the results in this communication.

First: With regard to the question of constancy—*i. e.*, is the presence of this organism in the river subject to seasonal variations?

It will be remembered that in the studies of Dunbar upon the spirilla of the Elbe at Hamburg it was found that with the advent of autumn and winter—*i. e.*, the onset of cold weather—the spirilla gradually diminished in frequency, and finally disappeared entirely from

[1] See Transactions of the Association of American Physicians, vol xi., 1896; also Journal of Experimental Medicine, 1896, vol. i. p. 419.

the water itself, though from time to time they were demonstrable in the mud from the bottom of the river.

Our studies, which have been continuous since June last, demonstrate the occurrence of spirilla in varying numbers in the water during all four seasons of the year. They were most numerous during the months of June, July, August, and September, after which they gradually became fewer, and during January and February of this year almost, though not quite, disappeared; becoming again more conspicuous with the beginning of March.

Whether the diminution observed during the autumn and winter months can be attributed to the low temperature of the water alone, we cannot say, but we incline to the opinion that this, together with the frequent flushing of the river and its tributaries, particularly the sewers, by the heavy fall rains, has much to do with it.

Second: As to the distribution of the spiralla in the river. We have isolated them from samples of water collected at points situated a short distance apart, from practically all that part of the river that is within the city. They have been found at both high and low tides. We have also obtained them from a number of main and branch sewers that empty into the river on either side. They have also been isolated from the water drawn from the laboratory faucets, so that their presence in the river above the Fairmount dam, that is above the points of greatest sewage pollution, is certain. Concerning this latter point, however, it must be remembered that the water of the Schuylkill river, as pumped into the city reservoirs and mains, to be used for domestic purposes, is already charged to a certain extent with sewage from towns located farther up the stream.

Third: Concerning the presence of this group of spirilla in other American streams, the time at our disposal has permitted the investigation of but one other source of supply, viz., the Delaware river. Here we encountered the spirilla as frequently as we did in the Schuylkill and under essentially similar conditions. The spirilla isolated from the Delaware river and the sewage emptying into it did not differ in nature from those found in the Schuylkill and its tributary sewers.

An interesting question that arises in connection with these investigations relates to the origin of these bacterial forms. We have, as stated, encountered them both in the waters of the two rivers and in

the effluents from sewers emptying into them. Do they occur in the rivers as a consequence of sewage pollution, or are they in the sewage as a contamination by the river water that in some cases backs into the sewers during high tides? We are inclined to the opinion that they are brought into the rivers with the sewage, but from what source they gain access to the sewage we cannot say. It would be interesting to know if in household slops, or in intestinal evacuations, either normal or pathological, such forms were to be commonly detected. We have always found them to be more numerous in sewage than in water from the middle of the rivers, but this might readily be referable to the more favorable opportunities that sewage, rich in nitrogenous matters, offers for their multiplication.

In all we have isolated one hundred and ten pure cultures of spirilla from the several sources mentioned. After subjecting them to the routine tests it was found that few or none of them were identical in every particular. At the same time they approached one another in so many features and to such varying degrees that we could not avoid the opinion that they were but modifications of some one more or less distinct species; in other words, that we were dealing with a group the individuals of which were related to each other in a way suggestive of the relation between the typical *bacillus colli communis* and the numerous varieties that are embraced within the so-called colon group of bacilli. For the sake of convenience, various attempts were made to classify them into sub-groups according to more or less conspicuous peculiarities, but in no instance has it been possible to draw sharp dividing-lines.

With regard to pathogenesis: because of the resemblance of these organisms to *vibrio Metchnikovi*, with which we are strongly inclined to think them either identical or very closely allied, pigeons were employed as the test object for their disease-producing powers. By this test we could readily divide them into two primary groups, viz., pathogenic and non-pathogenic, though many of the members of these two groups have a number of cultural characteristics in common. Many of those found to be pathogenic are but feebly so, and many of those found to be non-pathogenic possess most of the cultural characters of the fully and feebly pathogenic ones, indicating the probability of their being but attenuated specimens of the pathogenic group. We have been obliged, therefore, to subdivide these two primary

groups according to their disease-producing properties for pigeons, as follows:

1. Those that are distinctly pathogenic, causing death of the animal, and producing constant pathological lesions after a more or less fixed interval of time.

2. Those that are feebly pathogenic. These may or may not cause death of the animal, and the lesions resulting from their action upon the tissues are atypical.

3. Those that are non-pathogenic, but which possess, in a conspicuous degree, the majority of the cultural characteristics of those embraced within groups 1 and 2, especially the production of indol in considerable amounts.

4. Those that are distinctly non-pathogenic, and which differ in several of their cultural peculiarities from members of the other groups.

The organisms embraced within the fourth group may, perhaps, be regarded as forming a distinct class, for the reason that they all failed to give the indol reaction when tested with sulphuric acid alone, though with few exceptions this reaction was obtained when they were subjected to the action of sodium nitrite and sulphuric acid; that is to say, they have the power to produce indol, but not to reduce nitrates.

The cultures of the first three groups showed more or less marked indol-production upon the addition of sulphuric acid alone; those of the first and second groups most decidedly so, while with those in the third group the reaction was variable, being quite marked with some, with others less decided. They all had, therefore, the power of reducing nitrates.

These organisms may be formed into two groups according to the structure of their colonies in 10 per cent. nutrient gelatin. The first group comprises those individuals whose deep colonies are distinctly rosette- or mulberry-like, and which rapidly liquefy the gelatin on coming to the surface in the form of a funnel- or cup-shaped depression. The margin of these liquefying colonies is homogeneous, and their surface finely granular. The organisms forming the second group possess somewhat variable cultural features. The deep colonies are less distinctly rosette-form, and sometimes show thread-like bands that interlace over the surface and around the margin. After liquefaction has set in, the margin of the colony is less homogeneous than in those of the first group, the surface is coarsely granu-

lar, and masses of the colony are to be seen floating in the liquefied pit.

If we attempt to classify them according to some of their other biological characters, we are able to group them in several different ways, yet none of the groups so formed are very definite, and most of the individuals in one group are different from those allied with them under some of the other modes of grouping.

With regard to their growth on potato we may classify them into three groups: (1) those growing luxuriantly on potato; (2) those growing only sparingly, and (3) those showing no visible growth.

With regard to their development on Lœffler's serum mixture they fall into four groups: (1) those that rapidly liquefy the serum; (2) those that slowly liquefy it; (3) those in which liquefaction is so slight as to be doubtful, and (4) those that cause no liquefaction.

As regards indol-production it is possible to classify them into five groups: (1) those that show marked indol-production on the addition of sulphuric acid alone; (2) those that show feeble indol-production on the addition of sulphuric acid alone, but in which the color-reaction becomes very much intensified on the further addition of sodium nitrite; (3) those that show no reaction on the addition of sulphuric acid, but show marked reaction on the further addition of sodium nitrite; (4) those that show no reaction with sulphuric acid alone and only a slight reaction with sulphuric acid and sodium nitrite, and (5) those that failed to reveal the presence of indol when treated with both the acid and the reducing body.

With a few exceptions the individual members of the several groups formed in either of these ways are not identical in all respects. The type of organism most frequently encountered is identical with the vibrio that formed the topic of last year's communication, and at the time was designated as *vibrio Schuylkiliensis*.

The other organisms differed from this type in one or more characteristics. With some the variation is quite insignificant, with others it is more marked; while those that are most unlike this type still possess features which are common to the type, and in this way render definite grouping impossible.

The morphological characters of the different organisms also vary somewhat. They vary as to length and thickness, and also with regard to the length of spirals formed. Some of them rarely occur

as other than short "comma" forms, while others exhibit a tendency to develop as spiral threads comprised of three or four single commas joined together. Others are prone to grow into much longer spiral threads in old cultures. These morphological tendencies afford no assistance in our efforts at classification, because those that are alike from this standpoint are frequently unlike in their other peculiarities.

We have also endeavored to detect differences between these cultures through the employment of the specific reaction that occurs between certain pathogenic bacteria and the serum from animals infected with or artificially immune from them. For this purpose animals were rendered immune from several of the more conspicuously pathogenic members of the group, and the serum from them was tested upon the various cultures by the ordinary hanging-drop method now employed in connection with the diagnosis of typhoid fever. As far as these experiments have gone, we have not obtained a complete reaction, as indicated by agglutination of the individual bacteria and cessation of motion; the nearest that we have been able to come to this has been agglutination with only partial cessation of motion. The reason for this may be that our animals were not brought to a sufficiently high state of immunity, being protected from only about ten times the fatal intra-peritoneal dose.

At all events, the serum from such animals (guinea-pigs), as well as the serum from animals in the height of acute infection, did not in any case give us what we would regard as a typical and satisfactory reaction. Two of the cultures that were pathogenic, but which from their cultural peculiarities might be regarded as less alike than the remaining members of the group, were used to immunize guinea-pigs. After bringing the animals to a stage of immunity in which they resisted about ten times the fatal intra-peritoneal dose, the serum from the one immune from what we shall call type *a* gave the partial reaction with a large proportion of the cultures; while the serum of the animal immune from the type *b* gave the partial reaction with but a very small number of the cultures. The serum from the animal immune from type *a* gave no reaction with type-culture *b*, nor did the serum of animal *b* react with type-culture *a*. On the other hand, a number of the cultures reacted to some extent with both serums, and a smaller number were unaffected by either serum, though with one

exception the cultural peculiarities of these latter were essentially identical with those that gave the reaction.

As a result of our efforts to differentiate these cultures by further experiments upon animals, we have found that when guinea-pigs were rendered immune from a single more or less typical member of the group, they were at the same time immune from five times the fatal dose of all other pathogenic varieties.

In the light of the foregoing differential tests we are inclined to regard all the cultures obtained by us as varieties of a single species, the important characteristics of which are those given for the spirillum described by one of us (A. C. A.) in the paper presented to this society at its last meeting. The apparent absence of certain physiological functions, such for instance as those of indol-formation and nitrate-reduction, we do not, under the circumstances, regard as of the same degree of diagnostic importance as was formerly the case, for in the light of the experiments of Dr. Peckham, recently presented to the National Academy of Sciences, we know that these functions are liable to fluctuation, and that by special methods of cultivation they may often be restored to organiams from which, under the influence of environment, they were temporarily lost or very much diminished in degree.

The interesting and important outcome of these experiments seems to us to be the demonstration in the waters examined of spiral forms possessing characteristics that might readily lead one to mistake them for the genuine cholera spirillum, should the existence of suspicious intestinal disorders in the neighborhood appear to warrant such an opinion.

Many of the spirilla obtained by us are of the usual size and shape of the cholera organism; they produce indol and reduce nitrates; their colonies are sufficiently like those of the cholera organism to easily cause error; they are often without pathogenesis for pigeons when inoculated subcutaneously, a property common to the comma bacillus, while intra-peritoneal inoculation of guinea-pigs is fatal, and death is preceded by the gradual fall of body temperature that is seen to occur in these animals when inoculated in this way with virulent cultures of the cholera spirillum; and like the latter organism our spirilla are not pathogenic for rabbits.

While the pathogenesis of the typical members of this group for

pigeons at once distinguishes them from the spirillum of Asiatic cholera, the absence of this property from many of the attenuated varieties that at the same time often retain the property of infecting guinea-pigs by intra-peritoneal inoculation, when taken together with the striking similarity between their general biological peculiarities, renders a mistake quite possible.

It is our opinion that the only trustworthy distinction that can be made between many of these varieties and the genuine cholera spirillum is through the employment of either the specific reaction with serum from animals immune from cholera, or by Pfeiffer's method of intra-peritoneal testing in such animals. These latter methods have not been employed by us.

The desirability of more extended knowledge of the nature and distribution of the spirilla in our American surface streams we hope, by these studies, to have made manifest.

DISCUSSION.

DR. GEORGE M. STERNBERG: I want to make a single remark upon this paper, and that is, that I consider these researches, made at the time when there is no cholera in the country and when there has not been for years, extremely valuable. If they had been made at a time when cholera was prevalent in the country, it would have been considered that cholera-bacilli had been discovered in the drinking-water of Philadelphia.

CANCER OF THE STOMACH IN EARLY LIFE,

AND THE VALUE OF CELLS IN EFFUSIONS IN THE DIAGNOSIS OF CANCER OF THE SEROUS MEMBRANES.

BY GEORGE DOCK, M.D.,
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CASE. C. McK., aged twenty years, farmer, born in Michigan, was admitted to the University Hospital October 21, 1896. He complained of an "obstruction in the gullet," pain in the epigastrium, between the shoulders, and in the small of the back.

History. The family history is negative as to new-growths and tuberculosis. The father (aged seventy-five years) and mother (aged fifty-three years) are alive and well. There are four brothers and four sisters living and well.

The patient was well up to October, 1895, not having had the common diseases of childhood. At the time given he had a pain in the epigastrium and the lower part of the thorax so severe as to cause him to "double up." At the same time there was a choking sensation in the throat, and a good deal of mucus was raised. A week later difficulty in swallowing was noticed. The food seemed to stop in the throat, and an effort was required to pass it down. This persisted to the present time. Frequently the food comes up with some force as soon as swallowed. For some time it has been impossible to swallow solid food, except after careful mastication. The patient denies actual vomiting; says he has never vomited blood. For the first six months there were almost daily attacks of "cramp" in the epigastrium. In February the patient had measles. This left him weak, and he was unable to walk for three weeks. In March the abdomen began to enlarge. Much flatus was passed; the bowels were constipated. After that the patient improved, gaining strength; but in August he again became weak. Two weeks before admission the legs began to swell. From the beginning of the disease the patient had to pass water two or three times at night. During the last two weeks the quantity of urine has diminished. The appetite is good. The bowels are very constipated; sometimes there is no stool for two weeks.

Present condition, October 23, 1896: slender frame, of medium size; extreme emaciation; skin dry, harsh, very pale, as are also the visible mucous mem-

branes. No jaundice; no cyanosis. There is œdema of the legs, the dependent parts of the thighs, and in the back from the sacrum to the lower dorsal region. The œdema is soft; the skin over it is glossy. The nails are curved, but the fingers are not clubbed. The mind is clear; the voice weak. The special senses are normal; the eyes lustreless; expression weary. The tongue is small, smooth for the most part, but with irregular, elevated white patches on the middle and sides. The gums are red and slightly ulcerated.

The lymph-nodules in the supraclavicular regions are slightly enlarged. The thorax is long, narrow, and flat; the expansion slight, but symmetrical. Percussion of the upper parts of the thorax alike on both sides. In front the note is short and high pitched. In the back dulness begins on the line of the ninth dorsal spine on both sides. Auscultation reveals weak vesicular breathing all over, with no adventitious sounds. In the dorsal position the liver-dulness cannot be made out. On sitting up dulness is encountered on the fifth rib in the nipple-line, moving freely with respiration. An inch lower down tympanitic resonance is obtained.

In the left axillary line stomach tympany is found on the fifth rib. The apex-beat is in the fourth interspace, one cm. inside the nipple-line. Heart dulness begins in the third intercostal space, extends from the left edge of the sternum within a centimetre of the nipple. The sounds at the apex are weak but clear. The second pulmonary sound is accentuated. The radial pulse is small, soft, regular.

The abdomen is much distended, measuring thirty inches at the umbilicus. There is tympanitic resonance all over the front to within three finger-breadths of the os pubis. The right flank is tympanitic. In the left flank there is dulness up to the anterior axillary line. On sitting, dulness reaches to the umbilicus. There is fluctuation. Palpation of the abdomen negative, the walls being extremely tense. The splenic dulness, when the patient lies on the right side, is found in the normal position, measuring four by two centimetres.

Examination of the pharynx negative. A soft stomach-tube, 1.1 cm. in diameter, is swallowed easily for 39 cm. (from the upper incisors), but cannot be passed further. The tube shows no remains of food on withdrawal. [Patient has been on milk-diet since yesterday.] Larger olive tips on whalebone stem cannot be passed beyond the point mentioned, but one 9.5 mm. in diameter goes through after passing a firm but elastic obstruction behind, at the distance mentioned, measured on the stem. On account of the obstruction and the patient's cachexia no effort was made to test the stomach digestion.

Temperature since admission has been between 97.8° and 99° F.; pulse 90 to 104; respiration 20 to 24.

Urine (sample) turbid with urates, contains no albumin or albumose, or sugar; diazo-reaction negative. Sediment negative.

October 24. The patient has had no new symptoms. Has taken in the last twenty-four hours twenty ounces of milk. Weight 108 pounds. Aspirated

ascites with small syringe, removing 10 c.cm. of yellow, opaque alkaline fluid. Heat and nitric acid cause a large yellow precipitate. Acetic acid in excess causes a faint increase of the turbidity, and the addition of potassium ferrocyanide throws down a firm coagulum. Fehling's test negative. Solution of caustic soda clears up turbidity slightly, increased by the addition of ether, but ether alone produces no change. A small sediment obtained by centrifugalization shows numerous round or oval cells two to four times the diameter of a red blood-corpuscle, some much larger, very few small cells, and red blood-cells. The larger cells contain numerous bright granules, and some of them vacuoles, either one or many small ones or one large one, giving the cell a ring shape, with the nucleus more or less compressed.

No tubercle bacilli could be found. [A guinea-pig inoculated remained free from tuberculosis.]

Blood examination. Blood flows freely, thin and somewhat pale. Red blood-corpuscles 3,230,000. Leucocytes 6200. Hæmoglobin (Gowers) 40 per cent. Differential count (1030 cells): small lymphocytes, 3.8; large lymphocytes and mononuclear, 13.8; multinuclear, 80.5; eosinophile, 0.48; degenerate, 1.1. Punctured with a trocar above the pubes, removing 4700 c.cm. of fluid. The fluid is bright yellow; opaque; specific gravity 1010; alkaline. Albumin (dry by weight, after coagulating with heat and acetic acid, washing with large quantities of water, alcohol, and ether), 3.8 per cent. Biuret-test, after removal of albumin, negative. Bile coloring-matter test (fuming nitric acid) negative. Fehling's test negative. Diastase test negative. On extracting 100 c.cm. with ether, after the addition of caustic soda solution, a few small drops of yellow oil are obtained. Prolonged centrifugalization does not clear up the fluid nor produce a fat layer. On standing over night in a 250 c.cm. cylinder a white layer forms 3 mm. thick, which under the microscope shows small oily-looking globules soluble in ether.

The centrifuge brings down numerous cells such as were obtained before. These contain many bright granules and vacuoles of various sizes. Soda solution does not dissolve the granules at once, but after remaining in ether and alcohol half an hour nearly all the granules disappear. Acetic acid clears up the bodies of the cells and makes the nucleus distinct, but does not affect the granules. Iodine solution stains the nuclei and protoplasm as usual, but does not show the so-called glycogen reaction (either in fresh or dried preparations). Methylene-blue in watery solution added to the fresh sediment stains the nuclei, as in dried preparations.

The cells were spread on cover-glasses, dried in the air and fixed with ether and absolute alcohol, formol vapor and solution, heat, picric acid, and sublimate. Stained in various ways these show variations in size from 6.3 to 30 μ. The smallest, resembling small lymphocytes, are very few. About half the cells are about 15 μ in diameter, and there are many from 20 to 25 μ. Many masses containing three to twenty or more nuclei can be seen, in which neither acids, iodine, nor stains show any separation. The protoplasm is usually pale and granular or vacuolated. The nuclei are relatively large,

stain deeply, and show numerous karyokinetic figures. (See figures and explanation in the text.)

27th. Urine 380 c.cm.; dark red, clear, no albumin. The foam is yellow. Fuming nitric acid shows bile-coloring matter; there are a few cylindroids. The patient feels more comfortable. The scleræ and skin show slight icterus. The abdomen is still above the level of the ribs. The superficial veins are plain, but not distended. The abdominal wall is tense. There is resonance in front to the pubes and on the right side, dulness in the left side (on which the patient lies). Palpation negative on account of tense wall. Liver-dulness from the sixth to the eighth interspaces in the nipple-line. Œdema in the back as before. The hands were swollen early this morning, but are not now.

At 1 P.M. the patient vomited immediately after eating some bread and milk. There is diminished resonance in the back below the left scapula, with diminished breath-sounds and vocal fremitus. Aspirated in the ninth interspace at the angle of the scapula, withdrawing 10 c.cm. of clear yellow fluid. This contains cells like those in the peritoneum.

28th. Urine 450 c.cm.; specific gravity 1023; dark green with yellow foam; marked bile-color reaction. Sediment contains hyaline casts, sometimes with yellow granules. The jaundice as before. Liver-dulness from the fifth to the seventh interspace in the nipple-line. Abdomen tense as before. The heart is not displaced. The dulness in the left back as before; the half-moon shaped space is clear. Vomited a little mucus.

November 2. Urine 1100; specific gravity 1023; dark yellow. No albumin nor sugar. Diazo-test positive. Sediment negative. Weight 96 pounds. Patient has not vomited since the 28th. Eats a little bread and milk, corn-bread and beef-broth. The heart is not displaced. On the left, behind, there is dulness from the fourth dorsal spine, the upper line extending down and toward the front to the ninth interspace in the middle axillary line, where there is tympanitic resonance. In the right, posteriorly, there is dulness from the ninth spinous process to the seventh interspace in the axilla, sloping down to the liver-dulness in the mammary line. Breath-sounds and fremitus absent over areas of dulness. Aspirated in the seventh interspace in the left axilla, obtaining 430 c.cm. of dark yellow fluid, specific gravity 1012. The foam is yellow; bile-test positive. Aspirated in the seventh interspace below the right scapula, withdrawing 220 c.cm. of paler yellow fluid, also of specific gravity 1012. Foam white; bile-test negative. On both sides the lung could be felt as a hard body coming against the needle.

The patient, declining to remain longer in the hospital, passed under the care of my friend, Dr. P. J. Livingstone, of Caro, Mich.

The diagnosis, as given in a clinical lecture, was malignant disease, probably cancer, of the peritoneum, lungs and pleuræ, with growths either in the wall of the stomach, including the cardiac end, or else in the tissues behind it, and pressing on it; also growths pressing on

the bile-ducts. The primary seat was left in doubt. The absence of definite symptoms on the part of the stomach, intestines, pancreas, and other abdominal organs made it impossible to assign the primary seat to one of them. The impossibility of examining the stomach-digestion made accurate investigation of that organ impossible. The age made it most probable the disease was primary in the intestine. Primary so-called endothelioma of the peritoneum and pleura was considered, and also a primary growth in the retroperitoneal tissue. Tuberculosis was excluded on account of the low specific gravity of the fluid and the character of the cells. A primary growth of the œsophagus or cardia was excluded.

About a week after leaving the hospital the patient died, and Dr. Livingstone obtained an autopsy. Unfortunately, an accident early in the operation compelled Dr. Livingstone to leave and prevented a complete examination, as also the obtaining of much material. Dr. Livingstone writes that the wall of the stomach was thickened all over and so retracted that its capacity was not more than twelve ounces. The thickness extended to the œsophageal opening, and was especially marked along the greater curvature. Around the cardiac end were large adherent masses of carcinomatous lymph-nodules. The pylorus was almost entirely closed. The omentum was thickened and rolled up. The intestines were involved in a mass of adhesions with the enlarged mesenteric glands. The pancreas was also involved in the new growth. The rectum and bladder were free. The right pleura was adherent to the lower half of the lower lobe of the lung. The latter was of the color and consistence of liver. The pericardium and heart were not affected. The various body-cavities contained, together, five or six quarts of fluid. There was marked jaundice.

Questions in regard to the left pleura and the diaphragm could not be answered. The only tissues saved were a section of the pyloric end of the stomach, the gall-bladder with a bit of liver, and the right kidney and adrenal with peritoneum.

The pylorus has a small ulcer extending into the submucosa. The mucous membrane around the ulcer is thickened and with the submucosa measures 5 mm. in depth. The muscularis is 3 mm. thick. Continuous with this is a firm cancerous mass 1.5 cm. thick. Four cm. from the pylorus the mucosa is 1.5 mm. thick, the submucosa 5 mm., and the muscularis 1–1.5 mm.

The gall-bladder is retracted in all directions, being 2 cm. in diameter in the widest part. The surface is covered with small yellow nodules. The wall is from 1 to 4 mm. thick. The cavity is filled with thick white mucus. In the wall of the cystic duct, just beyond the gall-bladder, is a soft, white, roundish mass 3 mm. in diameter. Just beyond this is another mass, 1.5 cm. in diameter, obliterating the lumen in that part. Further down is a carcino-

matous lymph-nodule, and beside this is an infiltration which passes into the liver, with the veins. The peritoneum over the kidney and adrenal is from 2.5 to 5 mm. thick, filled with yellowish nodules or coalescent masses of considerable size.

Microscopical examination. Pylorus: the ulcer mentioned above extends into a scirrhous mass. The remains of the mucosa show for the most part a granulation-tissue filled with large cells with deeply staining irregular nuclei. Tubules are rare. The cells in them usually grow irregularly, filling the lumen. At the bottom of the mucosa are long, oval alveoli, lined by irregular cylinder-cells, the deeply staining nuclei of which are toward the walls of the alveoli. A few nuclei show traces of karyokinetic figures. There is no basement-membrane in these alveoli. The walls of the alveoli are made up of connective tissue with few long and narrow nuclei, and are sparsely infiltrated with small round cells. The submucosa contains a few small alveoli lined with polymorphous cells, but for the most part shows an extensive infiltration with shrunken cells in small places. In the muscularis are large areas filled with cells which have large, pale vesicular nuclei and very little protoplasm. These spaces sometimes show very thin lines of connective tissue traversing them in various directions, so forming alveoli. Beneath the muscularis are large and small alveoli, the walls of which are of dense connective tissue. They contain atrophic cells.

Near the pylorus the mucosa is still cancerous. The tubules do not show, but are replaced by a granulation-tissue containing epithelial, small, round and multinuclear cells and long spindle-cells. At the bottom of the mucosa are irregular alveoli, lined with irregular or cylindrical cells in a single or double layer, or irregularly filling the lumen. Cells with small nuclei and swollen protoplasm of fine granular or homogeneous appearance are sometimes present in the alveoli. Some of the alveoli are lined by long cylindrical cells with small, crescent-shaped nuclei close to the wall. The muscularis mucosæ here contains many alveoli, some of them passing through its whole width, of irregular outline. These are lined with a single layer of cylinder-cells, or more frequently are filled with irregular cells. Just below the muscularis mucosæ are alveoli filled with cells. These have deeply stained nuclei and a large amount of protoplasm, with round or oval outlines. The cells lie close together, so that the boundaries can only be seen by careful illumination and focussing. The cells are retracted from the walls of the alveoli. In some alveoli all the cells have relatively small nuclei and clear, swollen bodies. There are areas of multinuclear cell-infiltration in the submucosa, and extensive large-celled infiltration in the lymph-spaces. The muscular fibres are separated by alveoli filled with epithelial cells, with thin septa in the larger alveoli. There are also a few alveoli lined with a single layer of cylindrical or cubical cells and containing mucous-looking material in the centre. Just beneath the peritoneum are alveoli lined with cubical cells. A few free cells in the alveoli show mucous degeneration. In some the nuclei show evidences of recent cell-

division. Furthest away from the pylorus the mucosa shows tubules for the most part of normal appearance, though the cells are, as a rule, more advanced in mucous degeneration than in a healthy stomach. In a few tubules the cells stain unusually deeply. This is seen especially at the bottom of the tubules, and in some cases these tubules are prolonged through the muscularis mucosæ. The submucosa and muscularis show cancerous change similar to that in other parts already described.

The wall of the gall-bladder contains numerous small alveoli just beneath the serosa. The large mass described is a carcinomatous focus containing alveoli with very thin septa, and with cells resembling those of the other parts already described. The folds of the mucous membrane of the gall-bladder and cystic duct are filled with cancer alveoli. There are also foci of small-celled infiltration. The cancerous tissue passes into the liver along with the large vessels, and is found, also in portal areas, some distance from the surface.

The peritoneum over the right kidney and adrenal contains large alveoli filled with the characteristic cells. There is also much small-celled infiltration. The veins of the peritoneum are much distended.

This was evidently a case of cancer of the stomach primarily. That the disease began in the pylorus is impossible to prove, though highly probable. At all events, widespread infiltration or multiple new growths occurred, so that the whole stomach-wall was early involved, followed later by metastasis in the peritoneum and pleuræ.

This view is based on the character of the growths and their distribution. It is hardly necessary to exclude a primary so-called endothelioma of the peritoneum, as the growths here do not go out from the endothelial cells, as in the other disease. The early infiltration of the whole wall gave the local disease the character of a latent cancer, while the affection of the cardia produced the striking symptom of obstruction there.

The case presents two aspects of especial interest: the youth of the patient and the physical and microscopic characteristics of the fluid in the peritoneum and pleuræ.

AGE. It is not necessary to speak at length on the first point. Since the publication of Mathieu's[1] classical article, in 1884, it has been admitted more generally than before that cancer of the stomach can occur before the age of forty or even thirty, once looked on as the earliest possible periods. A number of cases have been reported by trustworthy observers. Many are published in so casual a way

[1] Mathieu, Marc: Du cancer précose de l'estomac. Paris, 1884.

that enumeration and analysis are out of the question. One fact of importance that seems to be demonstrated by recent observations is that cancer of the stomach in early life often has a slow course. This was brought out when, in the Société médicale des Hôpitaux, March 10, 1895,[1] Mathieu reported the case of a man of twenty-five years, who died of cancer of the stomach, whose symptoms began three years before. Catrin mentioned another case lasting two or three years. Ferrand spoke of a case with slow development in a young girl, but the diagnosis was not so positively made as in others. [Puncture of the enlarged liver withdrew a "juice manifestly cancerous."]

The present is the second case of gastric cancer in early life I have seen in which a positive diagnosis was made. In the other case there were classical symptoms in a woman of twenty-four years. A year later my colleague, Dr. B. E. Hadra, operated on account of complete obstruction of the pylorus, and we found the disease (scirrhus) limited to a ring including the pylorus, and only six centimetres wide at the widest part. There was no evidence of cancer in the lymph-nodules removed with the mass.[2] The matter of slow course is important because of the growing and proper tendency to look on cancer of the stomach as a surgical disease. It would be permissible to make a bolder attempt at complete extirpation of all diseased parts in a young person than in the usual subjects of gastric cancer.

It is hardly necessary to speak of the diagnosis of cancer of the stomach in early life, except to repeat the remark of Boas that the diagnosis is difficult because in young subjects cancer of the intestine is more frequent. Of course, in youth, as later, the cancer may be latent, or there may be early involvement of the whole wall, so obscuring the diagnosis or making it difficult.

THE EFFUSION. The transudate in the case now reported belongs to the fatty variety, the peculiarities and causes of which were first accurately shown by Quincke.[3] In the present case the milky appearance was due to fatty degenerated cells and free fat-globules from

[1] La Semaine médicale, 1895, p. 225.

[2] Since this paper was written I have received the report of the post-mortem examination, confirming the diagnosis made in another case in my clinic, in a woman of twenty-one years. Symptoms were present nine months; tumor was discovered six months before death. Operation was declined. Cancer of the pylorus was found, apparently without metastases.

[3] Ueber fetthaltige Transudate. Hydrops chylosus und Hydrops adiposus. Deutsches Archiv für klin. Med., Bd. 16, p. 121.

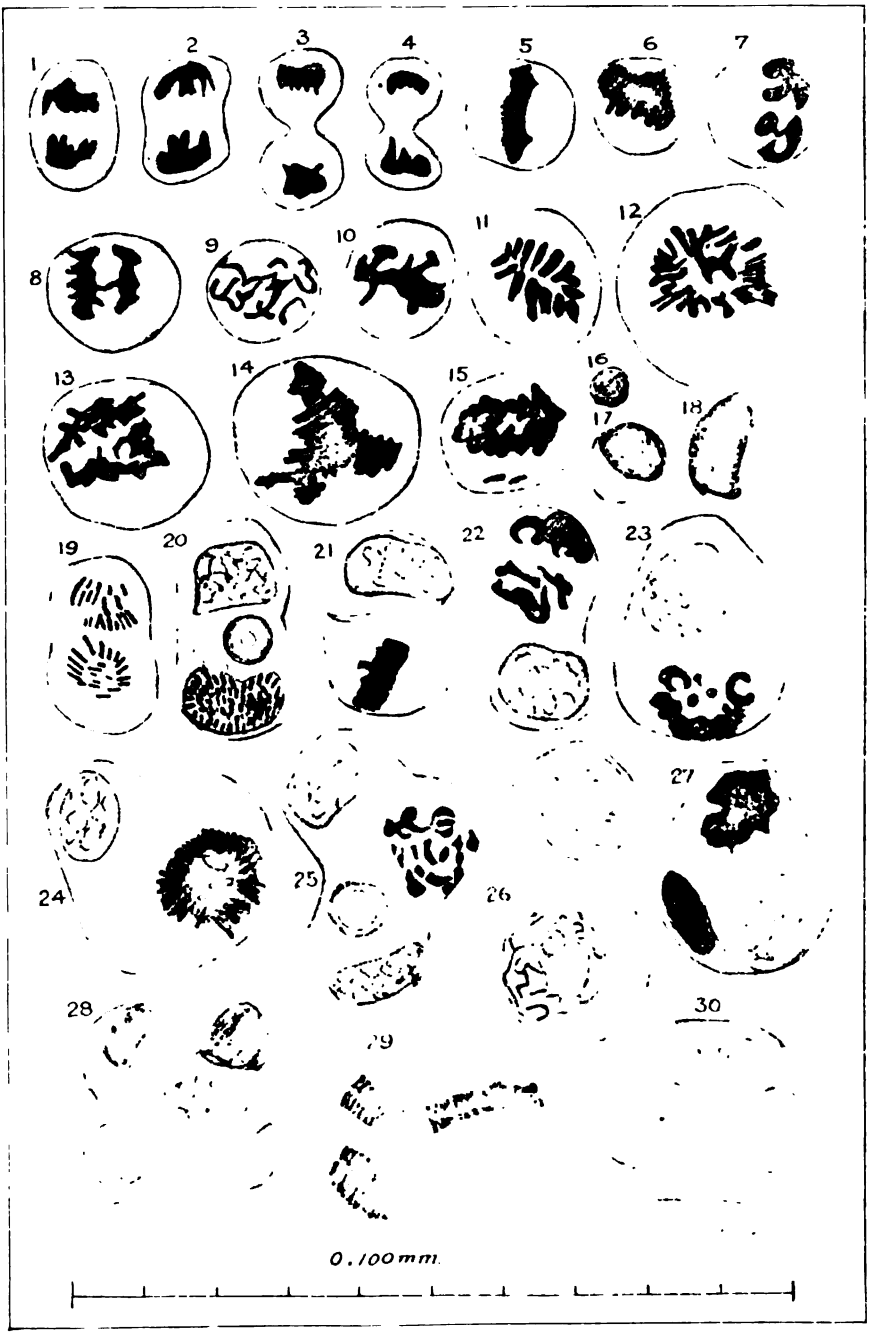
those cells. As this can occur in conditions so different as tuberculosis and cancer it evidently has only limited diagnostic value.[1]

The low specific gravity of the fluid, as in my case, is usually looked on as characteristic of cancerous as distinguished from tuberculous exudates. The latter are usually of high specific gravity—from 1022 to 1025, in my experience. But sometimes a cancerous effusion has a high specific gravity. In a case of carcinoma of the pleura secondary to one of the stomach, with fatty fluid, Bögehold[2] found the specific gravity of the fluid was 1021 to 1023. [There was considerable free blood in this fluid.] Quincke, in two cases of cancerous fatty ascites, also found a specific gravity of 1023. On the other hand, in tuberculous ascites the specific gravity may be as low as 1015. So the specific gravity of effusions must be used with caution in diagnosis.

THE CELLS. For the last fifty years the belief in a characteristic cancer-cell has slowly changed as objective criticism stripped away each attribute thought to be peculiar. At present there is little left but the unfulfilled hope that a cell-parasite may be found, by the recognition of which we may distinguish cancer-cells from others. Peculiarities of form or size, the presence of vacuoles, especially of large vacuoles, fat-granule-cells (especially these last two when in considerable number), cells containing glycogen, have all been abandoned on account of the uncertainty accompanying their application. So careful a clinician as Eichhorst still makes use of some of these things, however. In the last edition of his *Lehrbuch der klin. Untersuchungsmethoden*, Berlin, 1896, he says, "Especially in cancer of the pleura we find in the exudate, not rarely, abundant fatty-granule cells and cells with multiple nuclei, which are characteristic of cancer." Geigel and Voit speak with more caution, but much to the same effect (*Lehrbuch der klin. Untersuchungsmethoden*, Stuttgart, 1895). But most observers hold that only the recognition of distinct tumor-particles can be used in making a diagnosis of new growth of the serous membranes. The finding of such particles is, of course, not common.

[1] As the quantity of fat extracted with ether was so small it is possible the opacity was due in part to some other substance than fat. Rotmann, in a valuable article (Zeitschrift für klin. Med., Band xxxi. p. 438) quotes G. Lion, who found a casein-like substance as the cause of a milky ascites. Hammersten in a similar fluid found a mucoid body.

[2] Berlin. klin. Wochenschrift, 1873, No. 24, p. 347.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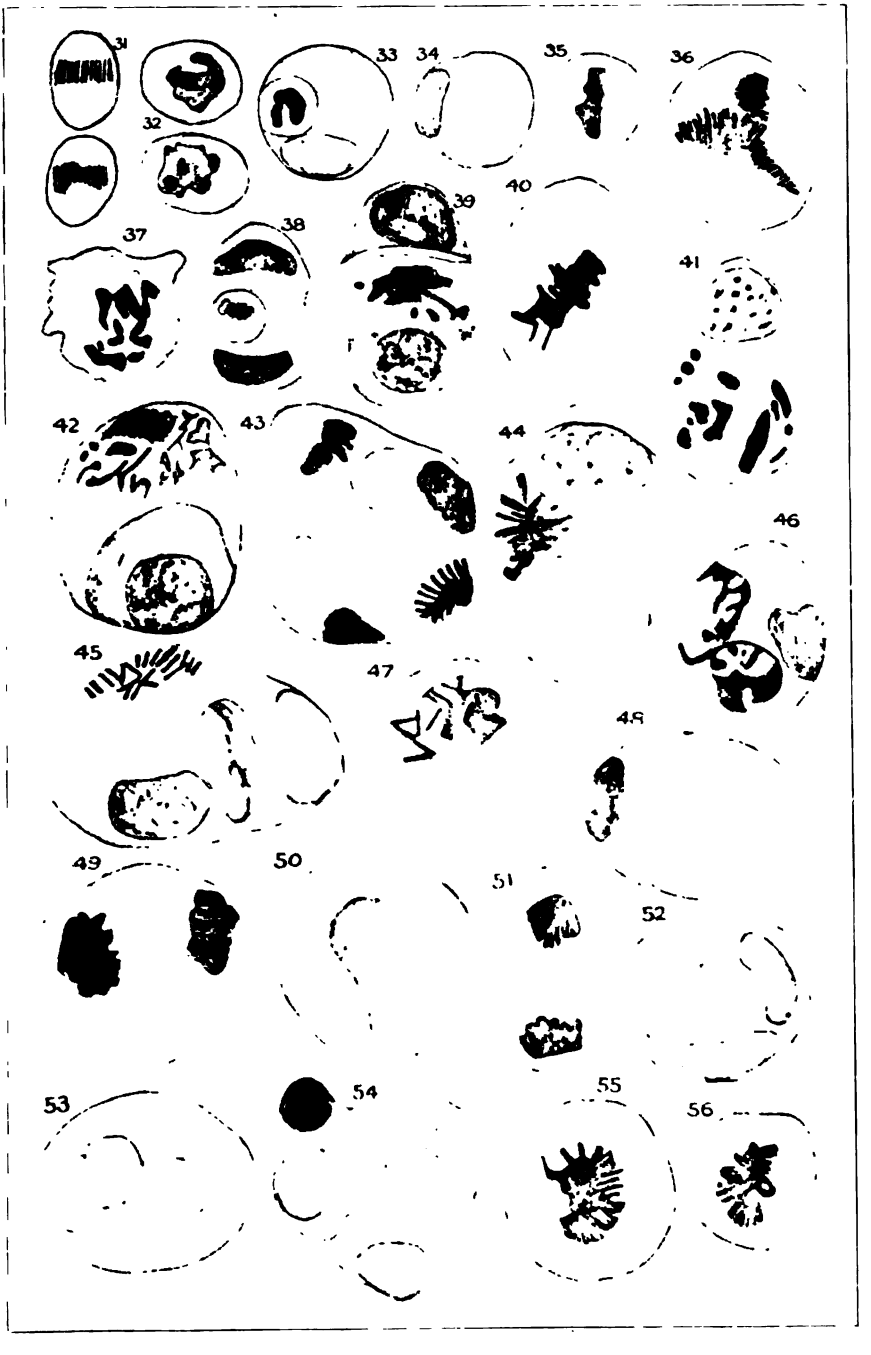
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It was, therefore, a matter of great interest when Rieder[1] reported a case in which he made a diagnosis of malignant disease of the peritoneum and pleura from finding numerous cells in the exudate showing indirect nuclear division. The patient was a woman of forty years. "Section showed sarcoma (carcinoma?) of the peritoneum, probably secondary to malignant disease of the ovaries." In the fluids obtained during life cells were found which were remarkable "in the first place, on account of the differences in size and shape of the individual cells. Often there were indentations and constrictions, sometimes buddings. In many cells there were one or many vacuoles, often so large that the nucleus was pushed to one side, sometimes hardly visible. The nuclei varied in size and number." The examination of the stained cells showed large numbers of cells showing indirect division, and especially cells with atypical mitoses. Rieder fully described and accurately figured these cells. His description should be consulted in the original by those interested, being too detailed for quotation here. I have found some interesting forms that he did not, and, on the other hand, he describes some forms I did not get to see. Thus, I did not see such beautiful multilobed cells as he shows, but I seem to have seen more of the atypical mitoses.

Incited by the excellent article of Rieder, I began to examine exudates and transudates more carefully than before, but the case now reported was the first one I encountered in which I obtained positive results. Other cases examined in the meantime were non-malignant.

I proceed to a description of the cells. After fixing the preparations were stained in various ways. The best results were obtained by the use of dilute hematoxylin solutions, especially after hardening in picric acid.

Cells having the size and appearance of lymphocytes are but rarely found (Fig. 16). Multinuclear leucocytes are also very uncommon. The fatty-granule cells that were so numerous in the fresh sediment appear after fixing as in Figs. 17 and 18. In these the nucleus stains with moderate intensity. It is usually finely granular or striated, sometimes shows a fine network, and rarely a nucleolus. The nucleus in these, as in other cells, sometimes contains small vacuoles (Fig. 23). The protoplasm is either finely granular or homogeneous, or, in cells suitably fixed, shows the fatty granules. The protoplasm does not

[1] Deutsches Archiv für klin. Med., Bd. liv. H. 6. p. 544.

take eosin well; with Ehrlich's neutrophile mixture it shows very fine neutrophile granules thickly filling the cell. [In the figures the protoplasm has been shaded without any attempt at a reproduction of the structure.] The vacuoles show well in stained preparations. They do not give the microchemic reaction for mucin with thionin or hematoxylin. They rarely reach a size larger than 25 μ in diameter, and vacuolated cells such as Quincke and others describe, 100 to 120 μ in diameter, I did not find at all. There are many bodies looking like giant-cells or aggregations of cells. Some are undoubtedly single cells with many nuclei, and I show some of the smaller ones in Figs. 24–30, 43–45. Others contain as many as twenty nuclei, but it is not possible to be certain these are not small cell-nests. However, in the fresh sediment they could not be separated by pressure on the cover-glass, nor could any boundaries be shown by silver nitrate. The latter test, however, on cover-glass preparations is very uncertain. The cells shown in Figs. 21 and 39 show incomplete division of the protoplasm. Occasionally cells showing a similar condition with three or four parts can be found.

The most remarkable feature of the sediment is presented by the great number of karyokinetic figures. These are especially common in cells from 12 to 18 μ in diameter. The protoplasm of these cells is usually more homogeneous than that of others. Vacuoles sometimes occur, and in rare cases the protoplasm may be very much degenerated. Mitoses are so numerous that every field contains one or more. Often two to five can be seen in a small field. Various stages of nuclear and cell division are present. The most common is that of the equatorial plate, as shown in Figs. 5, 6, 11, 15, 21, 27, etc. The spireme (Figs. 9 and 26) and the monaster (Figs. 24 and 44) are uncommon. The metaphase is not so easily recognizable, partly on account of the obscurity of many of the figures, but is well shown in Fig. 29. The anaphase is common, as in Figs. 1–4, 8, etc. The chromatic figures in about half the examples are fairly typical, or show such modifications of size and shape of the chromosomes as can be explained by slight alterations or the mode of preparation of the specimen. Chromatic figures are also found in larger cells, but having the same kind of protoplasm as the smaller one just mentioned, and hence not enlarged as the result of degeneration. These reach a diameter of 28 μ. Cells of all sizes, but especially the larger ones,

sometimes show atypical mitoses. Thus, Figs. 14 and 36 show tripolar nuclei. The nuclei in Figs. 12 and 13 may be atypical, but in the absence of polar bodies and achromatic figures they are difficult to interpret.

Cells containing more than one nucleus, and with the nuclei in different stages, are also common. Some of these are shown in Figs. 20–27, 39, 41–45. Many other varieties of these could be given. In these cells one or more of the nuclei are in the resting stage, and one or sometimes more in various stages of indirect division and sometimes showing an atypical figure. The cells in the pleural transudate resemble in all respects those found in the peritoneum, as a few figures will show (Figs. 31–45).

The mitoses found, so far as they can be studied by the chromatin alone, show all the common abnormalities. Thus we find hyper- and hypochromatic nuclei, the latter being rare. Giant mitosis may be represented by the tripolar figure in Fig. 14. Asymmetrical mitosis is not easy to recognize on account of the imperfect preservation of the chromosomes in many cases. The examples of mitosis in multinuclear cells resemble often the figures given by Krompecher.[1]

The finding of the mitotic figures in the ascitic and pleural fluids may be considered from two separate aspects, viz., the great number of these in the first place, and the presence of atypical forms in the other. I shall consider the last first.

The interesting history of atypical mitosis can only be touched on here. Eberth[2] was the first to describe division into four parts, but his statements were at first discredited by Flemming and Strassburger. Later, however, Arnold[3] found multiple karyokinesis in carcinoma. He thought the process might result in the production of polynuclear cells. Since then a great deal of work has been done on the subject, much of it being excited by the ingenious speculations of Hansemann. From an examination of the work done so far it appears that atypical mitoses are found in various pathological conditions, not only in new growths like cancer and sarcoma, but also in benign tumors and in regenerations; in short, "in all tissues of strong reproductive activity and when there is active mitosis (Ströbe)." They are also found in

[1] Ueber die Mitose mehrkerniger Zellen und die Beziehung zwischen Mitose und Amitose, Arch. für path. Anat. Bd. cxlii. p. 447.

[2] Archiv für path. Anat. und Physiol., Bd. lxvii. [3] Ibid., Bd. lxxxiii.

tissues irritated by various poisons, such as quinine, chloral, nicotine, etc., or in tissues exposed to high temperature (Galeotti). In cancer all observers find them in great richness and variety, but the view that the presence of even a large number of pathological mitoses in a tissue justifies the diagnosis of cancer is gradually being abandoned.[1]

As regards the occurrence and importance of mitotic figures in exudates and transudates, I can find nothing in the literature except the article of Rieder. I have endeavored to control his findings and my own, as far as I was able, by examining other similar fluids in the same way. The results are interesting, but, of course, much more research is still necessary.

I find that in ordinary serous effusions, as in serous pleurisy and tuberculous peritonitis, the large majority of cells are multinuclear leucocytes. There are also few or many small cells having the characteristics of lymphocytes, a few larger, mononuclear, cells usually with small vesicular nuclei, and in some cases fibroblasts. My examinations in such fluids, therefore, give the same results as were obtained by E. Grawitz[2] in his investigations on the formed constituents of pleural exudates. Cells like the smaller forms in mitosis in my own case are not found in such exudates. The larger cells in my case do not have their counterparts in ordinary exudates. As I surmised they might be endothelial cells from the peritoneum and pleura, I obtained bits of the former tissue at operations on the abdomen, made cover-glass preparations of scrapings, and examined these after treating them as I had the sediments. In this way, from normal peritoneum and from the apparently normal peritoneum in tuberculosis of that membrane, cells may be obtained which resemble in form, size, and structure of nucleus and protoplasm the larger cells in my case of cancer, but without mitoses. From the inflamed appendix vermiformis I obtained similar cells, also with resting nuclei, but the cells on inflamed surfaces are often smaller than those from similar parts

[1] Although I have not thought it necessary to give a detailed review of the subject of atypical mitosis, I should add that a study of the literature will be very helpful to those who wish to make investigations in effusions. As all the literature is quoted in the indispensable works of Hansemann (Arch. für path. Anat., Bd. cxix. p. 299, Bd. cxxiii. p. 356, Bd. cxxix. p. 436; Studien über die Spezificität, den Altruismus und die Anaplazie der Zellen, Berlin, 1893), Ströbe (Beiträge zur path. Anat., Bd. xi., xiv.), Cornil (Journal de l'Anat. et de la Physiol. norm. et path., 1891, t. xxvii. p. 97), and Galeotti (Beiträge zur path. Anat., Bd. xiv., xx.), it is not necessary to give a complete bibliography here.

[2] Charité-Annalen, xviii. Jahr., p. 265.

in health. From the normal serosa I obtained cells apparently showing amitotic division. These are more numerous on the inflamed peritoneum or pleura, and I figure one of the most striking examples (Fig. 50) from the latter. Several similar specimens, as also some showing later stages, were seen.

In two cases I found cells more like the peculiar forms in my case of cancer.

One of these was a woman of fifty years. A cancerous mamma, with extensive metastases in the axilla, had been removed. A few days after the operation effusions came on in both pleural cavities, with adhesive pericarditis. Femoral phlebitis then developed, apparently from an old leg ulcer, and about two weeks after the operation the patient died. The pleural effusion was examined the second day after it began—*i. e.*, after the disappearance of friction. It was turbid, contained an excess of red-blood cells and lymphocytes, large numbers of multinuclear and a few endothelial cells. The latter showed fatty degeneration, breaking down of the protoplasm, with the formation of small blebs on the edges, and small and large vacuoles. Many of the large cells contained multinuclear cells in vacuoles, a process seen very rarely in the case of McK. (Fig. 33). Some of the larger cells contained two or three or more nuclei in the resting stage. Some of these cells showed partial division of the protoplasm (Fig. 54). Besides these there were a few cells, about two or three in each preparation, showing karyokinesis. These cells are from 20 to 25 μ in diameter, and resemble the larger forms found in the case of McK. The figures are fairly typical, the chromosomes preserved better than in McK. (Figs. 55, 56).

The body of this patient was examined post mortem by Dr. A. S. Warthin. He found under the pulmonary pleura a few small, puckered nodules. To the naked eye the pleura was intact. Microscopic examination showed these to be small-celled scirrhous foci immediately beneath the pleura, the latter being intact.

In another case pleurisy developed in a young man some weeks after removal of a diseased appendix. Symptoms previous to the appearance of the pleurisy made it seem probable there was a subphrenic abscess; but as the patient left the hospital before death the exact relations could not be made out. The fluid from the pleura was slightly turbid, specific gravity 1024, and gave a growth of streptococci. It contained large numbers of pus-cells and red blood-corpuscles; many small endothelial cells up to 18 μ in diameter, with well-preserved protoplasm; larger cells up to 30 μ in diameter having normal protoplasm; most of these larger cells contain either two or more nuclei in the resting stage (Figs. 52, 53), or a single nucleus in direct division (Fig. 50); a few of the smaller specimens (20 μ in diameter) show karyokinetic figures, but the larger ones (25–30 μ) are found with them more frequently (Figs. 46, 47, 49, 51). Finally, there are cells with the protoplasm occupied by a single large vacuole, the nucleus usually

pressed to one side (Fig. 48). These cells measure as much as 55 μ. The nuclear figures are sometimes difficult to interpret, but, on the whole, are more regular than those of McK.

It seems, then, from the few cases examined, there are more cells showing mitosis in cancerous effusions than in those of simple or tuberculous inflammation. There may also be many atypical mitoses in the former case. The examination of the last case mentioned shows that the differences are quantitative and not qualitative. This is what we should expect from the knowledge we have of karyokinesis, normal and pathological, in tissues. From the results obtained by Rieder and myself it should often be possible to make a diagnosis, especially between cancer and tuberculosis of a serous membrane, by an examination of the cells in effusions. The results in the last case show that all other differences are less reliable than this one. I do not speak of inoculations. Aside from the risk of failure, the element of time may be important.

It is interesting to speculate on the origin of the larger cells found. These can hardly be other than endothelial. In Rieder's case and my own such cells are often in mitosis. This would seem to be the result of an irritation of the serous membrane, but an irritation that is not peculiar to malignant new growths, as my last case shows. We cannot, therefore, hope to determine the precise histological character of a growth on such a membrane from isolated cells from it. The fact is interesting in connection with the old view that in cancer of serous membranes the cells of the latter become infected, and so take part in the new growth, an idea of course now abandoned.

In all my cases I have examined the fresh sediment for possible parasites, hoping that a considerable experience with many parasitic protozoa would be of assistance. I could see nothing, however, suggesting such organisms. I looked with especial interest for the *Leydenia gemmipara*, described by Schaudinn in cases of cancerous ascites, but without success. In stained preparations inclusions are not uncommon, but nowhere do they suggest definite forms of parasitic organisms.

Explanation of the Plates.

All the cells were drawn with the camera lucida, using a Zeiss one-twelfth inch oil-immersion objective, No. 2 eye-piece. The scale is shown on Plate 1 by 0.100 mm. drawn from a standard scale under the same conditions. The outlines of the cells and nuclei are as accurate as possible. Peculiarities of the protoplasm have not been reproduced, in order to avoid confusing the picture.

Figs. 1–30 are from ascitic fluid in the case of McK.; Figs. 31–45 from the pleuræ in the same case. Figs. 46–53 are from pleurisy following appendix operation. Figs. 54–56 are from terminal pleurisy in a case of subpleural carcinoma of very limited extent. Further description of the cells is given in the text.

DISCUSSION.

Dr. Simon Flexner: A young person came to autopsy in the Johns Hopkins Hospital. There was a large tumor of the mesentery extending into the intestine. The peritoneal cavity contained several hundred cubic centimetres of a turbid fluid. The microscopical examination of this fluid showed great numbers of rapidly dividing cells, which were thought to be of endothelial origin. I did the autopsy. The cells were so remarkable that I called Dr. Welch's attention to them, and he said that a probable diagnosis of carcinoma could be made from these cells alone. Some days later I was able to work up the case more fully, and it proved to be a case of primary tuberculosis of the peritoneal glands. Yet from the appearance of the cells at the autopsy I felt confident that it would prove to be one of cancer.

PNEUMONIA IN PRIVATE PRACTICE.

By M. HOWARD FUSSELL, M.D.,
of Philadelphia.

The reason for this paper may be found, perhaps, not in any new or startling discoveries in regard to the pathology or treatment of pneumonia, but because the observation of all conditions in private practice must of a necessity be somewhat different from that had in hospital practice; and the writer has thought it worth while to record his experiences with pneumonia.

The paper is based upon cases of pneumonia, all seen in private work, in which fairly accurate notes have been made at the bedside. The number of cases is not large, but I have thought it sufficiently so to be of interest and value to the Association.

The number of cases observed is 134, with 24 deaths, a mortality of 17.9 per cent.

The mortality corresponds closely to that stated by Wells in his collected cases; that is to say, 18.1 per cent. When I saw the statement in Prof. Osler's *Practice* that "pneumonia is one of the most fatal of acute diseases," it gave me a mental shock, for, while I was, of course, aware of the percentage of mortality, I was so accustomed to seeing individuals, especially children, so remarkably ill with pneumonia and finally recover, that I had come to think that there must certainly be some mistake. The figures of my own cases, however, show that, taking all the cases together, the mortality is great, 17.9 per cent.

Eight of my cases were of the age of one year or *under;* of these five died, a mortality of 62.5 per cent.

The cause of death in most of the infants appeared to be the accompanying capillary bronchitis.

Eleven cases were two years old; none of these died.

Twenty-one were three years old, with five deaths, 23.3 per cent.

Ten were four years old, with two deaths, 20 per cent.

Five were five years old; no deaths.

Nine were six years old, with no deaths.

Five were seven years old; no deaths.

Three were eight years old; no deaths.

One was nine years old; recovery.

Between ten and twenty years, inclusive, there were nine cases; all recovered.

Between twenty-one and thirty years, inclusive, there were eighteen cases, with two deaths, 11.1 per cent mortality.

Between thirty-one and forty years, inclusive, eight cases, with two deaths, 25 per cent.

Between forty-one and fifty years, inclusive, thirteen cases, with three deaths, 23.07 per cent.

Between fifty-one and sixty years, eleven cases with three deaths, 27.2 per cent.

There were two cases over sixty years of age, neither of which died. Both of these cases were remarkable instances of the severe lesions which may occur and the individual still survive, and are worth special notice.

Case 132 was a woman of seventy-two years, with marked mitral regurgitation, but a perfectly compensated heart. She was suddenly seized with chill, pain in her right side, and high fever. On my first visit there were signs of beginning consolidation. The case ran an ordinary course, with consolidation of the whole right lung. The heart never faltered, and ended by crisis on the seventh day. This occurred ten years ago, and the woman is still alive. It should be noted, however, that the patient never recovered her usual vitality. She had been an unusually sprightly woman up to her illness, but since has been barely able to attend to her housework.

Case 133 occurred in a woman of eighty-six years, suffering from advanced organic disease of the heart. She was suddenly seized with fever, which lasted three or four days. Consolidations of the right base occurred. She seemed somewhat worse than usual for awhile, but soon was in her usual condition. The consolidation entirely cleared up, and the patient lived eight weeks, to die of failure of compensation.

Cases 128 and 130 were much of the same character.

It would appear from this list that in an ordinary practice, then, more than half the greater number of cases occur before the age of ten years, and that the greatest mortality is before one year, 62.5 per cent.

Between five and twenty-one years there were no deaths in thirty-two cases.

CAUSES OF DEATH.—Cases 96, 117, 118, and 130 each were hard drinkers, with the cardiac and circulating change which accompanies such. Three were over forty-five years of age.

Cases 107, 124, and 125 had advanced cardiac disease.

Case 123 was in a woman of over fifty years of age, a case of moderate severity. Her sister had just died. A niece was extremely ill with typhoid fever, and on the morning of the fourth day, while the patient was resting quietly, a "friend" made her appearance, told her she was very ill, that she would probably die, and should make her will. The patient immediately collapsed, and died in twenty-four hours.

Cases 105 and 106 were both pregnant women, aborted, and immediately collapsed.

Case 99 was in one of three non-resistent fat individuals, who are apt to die under any strain. Death occurred on the fourth day.

Case 66 had been allowed about the home without medical attention for several days of illness; when seen there was general collateral œdema, and death occurred in a few hours.

Cases 17, 18, 19, 38, 39, 42, and 49, were in healthy children who succumbed to the attack without any cause other than the disease.

Cases 1, 2, 3, 4, and 5 were infants under one year.

SEX. Sixty were males, with thirteen deaths, a mortality of 20.1 per cent.

Seventy-four were females, with ten deaths, a mortality of 13.7 per cent.

THE FAMILY HISTORY in all the cases was without any influence on the cause or result of the cases.

PERSONAL HISTORY. There was no peculiar history in the great majority of cases which seemed to have a causative influence.

CONTAGION. I saw four cases at one home in consultation, not in-

cluded in this list. The father was first attacked. The other cases followed at periods of about a week.

Cases 21, 30, 67, and 79 of this list were each followed by a case of pneumonia in the same house. In none of these instances did there seem to be anything about the premises to suggest a common cause.

Four or five cases, the result out of one hundred and thirty-three, however, is not a large number, if the disease is actually contagious, and the four cases may easily have been coincidences.

In all the cases there was the freest sort of communication among the various members of the family. Often a child was sick in a room where two or three others were compelled to sleep. None of these, with the above exceptions, developed pneumonia.

There is, then, absolutely no proof in these cases of any contagion by the ordinary means of transmission at least.

Whooping-cough was a cause in four cases, measles in two. All of the others were from entirely unknown causes.

Seven of the cases were alcoholics, four of these cases died.

Five were the subjects of valvular disease of the heart, two died.

Three women were pregnant. They all aborted, and two died.

There was one the subject of diabetes, woman of forty years, and one a child of seven years of nephritis. Both recovered.

DURATION. From first symptoms to crisis varied from one day to fifteen. In sixteen crisis occurred on fourth day, on fifth day in eleven, on sixth day in eight, on seventh day in twenty-seven, on eighth day in nine, on ninth day in twelve.

SEAT OF LESION. The right base in twenty-seven cases; five deaths.

The right apex in twenty-seven cases; three deaths.

The left base in forty-one cases; six deaths.

The left apex in four cases; no deaths.

The entire right lung in fifteen cases; four deaths.

The entire left lung in five cases; one death.

Both lungs in ten cases; six deaths.

The greater the amount of lung involved the greater the mortality, without reference to any other cause.

SPECIAL SYMPTOMS. *Signs of meningitis* occurred in five cases, all in children under five years of age.

In two cases the apex alone was affected, in two the base, and in one the entire lung.

These symptoms consisted in much delirium, opisthotonus, strabismus, and in convulsions. In some of the cases, indeed, the symptoms were so severe that a diagnosis of tubercular meningitis was made.

This was the fact, especially in Case 14, a child of two years, with healthy but careless parents. Had whooping-cough, and was suddenly seized with severe high fever. On examination the right apex was found consolidated; a diagnosis of pneumonia was made. On the third day the child had a convulsion, followed by marked strabismus, entire loss of sight, opisthotonus, and muscular twitchings, with the thumbs drawn into the palms. Considering the history of whooping-cough, with the remarkably limited consolidations at the apex, it was decided that the child had meningitis of tubercular origin. On the tenth day, however, crisis occurred, and following that the meningeal signs gradually disappeared. The child now, five years after the attack, is a strong, vigorous boy.

Meningeal signs of course are well known. They are usually spoken of as occurring with lesions of the apex. In two of these cases, however, the base alone was affected.

The lesson to be learned from the case just quoted is that, even in the face of the most positive symptoms, meningeal signs accompanying pneumonia may usually be considered as symptomatic.

Irregular Temperature. In several of the cases the temperature was so markedly irregular, actually intermittent, physical signs were delayed, that a diagnosis was not made for a period of three or four days, This was especially true in a case which terminated fatally. The boy, aged six years, was said to have fever. I saw him in the morning; the temperature was 98.4°. The next morning I found him out of bed, running about the house, with a normal temperature and absolutely no symptoms, but with a history of having had fever the previous evening. The next morning there was a slight fever and some cough. From that time on the temperature became higher, marked physical signs developed at the right apex, consolidation spread rapidly through the entire lung, and the patient died on the tenth day.

Early Physical Signs. The physical signs of an advanced consolidation are too well known to need repetition here. It has seemed to me, however, that the very first signs in the lung about

to be consolidated are dulness on percussion, with the breath-sounds decidedly weaker over the affected area than over the healthy tissue. These are far more constant in my experience than the famed crepitant râle, which, when present, while a sign of beginning consolidation, is far too often absent to be of any great value.

Signs of Crisis. In a number of my cases I have observed a few fine râles of beginning resolution occur before the crisis, and have been able to state correctly in a number of cases by this sign that crisis would probably occur within a few hours.

State of the Tongue. In the days of exactness in diagnosis it may seem old-fogyish to refer to the tongue of pneumonia, but the thickly coated white tongue with papillæ only less prominent than in the first stage of scarlet fever, with a red tip and edges, is often the first sign which makes a pneumonia thought of. It is certainly quite as characteristic and much more constantly present than the famed expiratory moan.

Fear of falling is another most characteristic symptom of pneumonia in children. In the first few hours, or even days, of illness, before physical signs are evident, a child will have the constantly high fever, will lie still if undisturbed, but the moment it is lifted it clutches at the nurse and manifests great fear, apparently fear of falling. This symptom has become to me almost pathognomonic in children.

Pain in the Abdomen. Children constantly answer when questioned where they have pain, by placing their hands over the abdomen and saying they have stomach-ache.

I once made a post-mortem for an esteemed friend in a case where the child had been unmanageable; physical examination was impossible, and the only symptoms were irregular fever and abdominal pain, with much abdominal distention. A diagnosis of "enteritis" had been made. The autopsy showed a consolidated lobe with empyema.

I have just seen a case of complete consolidation in a child of six years, where the only complaint has been abdominal pain, with temperature from 100° to 102° F.

This pain is of necessity referred from the irritated intercostal veins at the site of the inflamed pleura. Its cause is the same as the expiratory moan.

Delayed Physical Signs. It is a notorious fact that the physical signs of pneumonia in children are anomalous. They may be almost

indefinitely delayed, making their appearance only when the child is almost convalescent.

This may be true in adults so far as delay is concerned.

In Case 77, a girl of thirteen years, there were no definite physical signs until the fourth day, when they appeared suddenly.

In Case 92, a man of twenty-six years, the physical signs did not occur until the fourth day, and the symptoms and history were more those of beginning typhoid fever. Only careful, repeated physical examination allowed a diagnosis.

Complications. Nephritis occurred in two cases; both recovered from the pneumonia, and both casts and albumin disappeared from the urine in about one week after the crisis. The nephritis was only discovered by a routine examination of the urine, gave rise to no symptoms, and was not treated.

Empyema resulted in a child of six years, after what was apparently an ordinary attack of pneumonia of rather severe type. Recovery occurred after tapping and draining.

Delayed resolution occurred in three cases. The consolidation still exists in one individual.

In none of the cases was tuberculosis a sequel.

PROGNOSIS. In an acute disease, with a mortality of 18 per cent., the prognosis must necessarily be grave. But given an individual in private practice, between the ages of two and thirty years, with a sound heart, and a person not given to intoxicants, one can, with a good deal of assurance, foretell recovery.

It must be remembered, however, that there are certainly two effects of pneumonia—the local lesion and the systemic poisoning.

Numbers of cases have extensive lesion of the lungs, and, aside from the discomfort consequent upon the laming of so important an organ as the lung, seem to suffer but little. Others, with comparatively limited local lesion, are so badly poisoned that they succumb almost at once.

TREATMENT. In a disease where fully one-half are entirely unaffected by any remedy, where cases recover constantly that are never under the care of a physician, one must speak with great diffidence of the value of his remedies, especially of drugs.

I believe thoroughly that much good can be done by treatment; that it is criminal to allow a case of pneumonia to be wholly without

treatment; but I also believe that drugs or local applications have absolutely no effect upon its course. In my experience, borne out, I believe, by the cases I herewith submit, the treatment necessary consists of rest and care of the heart.

Rest is essential. Case 124 was doing well, there was no sign of collapse. I saw her at 10 A.M., with temperature normal, a slow, steady pulse. She arose from bed, walked about the room, and in two hours was dead, from failure of the circulation.

I have just seen a case in consultation which is not included in this list, but where resolution was taking place. Temperature was normal. The patient was violently delirious from post-febrile delirium. Her heart, which had been good, became rapid and irregular. A few hours' rest, obtained by morphine, caused the heart to become regular, and the patient is now well on the way to recovery.

Rest should be absolute, the patient not being allowed to rise to stool, but using a bedpan.

If the patient is delirious, morphine should be used, preferably hypodermically. It has the happiest effect.

I once acted as nurse to a noted homœopathic physician who could not be retained in bed; he was maniacal, attempting to climb out the window, etc. His pulse was running. A hypodermic injection of one-eighth grain of morphine put him to sleep, his pulse fell 20 beats to the minute, and was for the time much improved. A consultation among his homœopathic attendants resulted in his detention in bed "by physical force." The delirium continued, and the patient finally died.

The next important injunction is care of the heart. Of course, rest is the prophylactic measure. When, in spite of absolute rest, the heart begins to fail, strychnine, digitalis, and whiskey must be used. Strychnine used hypodermically will frequently abort a threatened collapse and carry a heart over the crucial period. It has been said that such treatment can do no good because it is but a whip to the jaded horse. That it is the whip is true, but if the horse can be made to make an extra effort to pull the load over the incline, the treatment may be safely disposed of. In all cases of impending heart failure I give strychnine in doses of one-twentieth grain every three hours hypodermically.

Summary of Cases.

Name.	Sex and age.	Family history.	Personal history.	Duration.	Seat of lesion.	Special symptoms.	Pulse	Respiration.	Temperature.	Result.	Post-mortem	Treatment.	Remarks.
1. Katzenbach.	M. 4 mo.	Good	.....	3 days	Right lung.	Urgent dyspnœa.	160	130	100	Death.	.....	Digitalis, ammon. carb. poultice.	Capillary bronchitis.
2. Brinsing,	F. 4 mo.	Good	.....	3 days	Both lungs.	Cyanosis.	160	...	103	Death.	.....	Digitalis, ammon. carb. poultice.	
3. G. Schofield,	M. 7 mo.	Syphilis.	.....	11 days	Right lung.	Several convulsions.	...	...	..	Death.	Entire convol. rt. lung.	Bromides, digitalis.	Apparent improvement tenth day; death on elventh.
4. Williams,	F. 9 mo.	Good	.....	2 days	Right apex.	Cyanosis.	160	88	...	Death.	.....	Nitroglycerine digitalis	
5. Scheet,	M. 10 mo.	Good	.....	7 days	Left base.	.....	...	...	...	Death.	.....	Digitalis ordered; none given.	Utter neglect of all directions.
6. Sterrett,	F. 1 yr.	Good	.....	5 days	Left apex.	.....	...	...	103	Recov.	.....	Simple cough mixture.	Rapid recovery.
7. Pester,	F. 1 yr.	Good	.....	9 days	Right lung.	Strabismus, blind, meningeal signs.	...	...	105	Recov.	.....	KBr, digitalis, cotton jacket.	Rapid recovery.
8. Ward,	F. 1 yr.	Good	.....	7 days	Right apex.	.....	...	...	104	Recov.	.....	Expectorants.	
9. M.	F. 17 mo.	Good	.....	3 days	Left base.	.....	...	...	...	Recov.	.....	Expectorants.	Scarcely ill.
10. Slater.	M 2 yrs.	Syphilis.	.....	6 days	Right apex.	Bronchitis.	...	...	104	Recov.	.....	Digitalis.	
11. Ferguson,	M. 2 yrs.	Good	Exposure.	5 days	Left base.	None.	...	...	...	.....	.....	Expectorants.	
12. D.	M. 2 yrs.	Good	.....	4 days	Right base.	.....	...	...	104	Recov.	.. ..	Expectorants.	
13. Merrick,	F. 2 yrs.	Good	.....	3 w'ks	Right apex.	Septic temperature.	...	...	104	Recov.	.....	Digitalis, strychn., cotton.	Temp. fell to normal in one week, then rose and fell at intervals for three weeks.
14. Metzler,	F. 2 yrs.	Good	Measles.	2 w'ks	Right apex, l. base.	.....	...	...	...	Recov.	.....	Supporting treatment.	Resolution delayed; seems to be two distinct attacks.

15. O'Hara,	M. 2 yrs.	Good	Whooping-cough.	2 w'ks	Right apex.	Meningeal signs.	...	...	...	Recov.	.....	.....	Opisthotonus, strabismus, blindness, diagnosis of tubercular meningitis.
16. Ward,	M. 2 yrs.	Good	Bad hygiene.	1 week	Right apex.	.....	...	...	...	Recov.	.....	Digitalis, cotton.	Bad nursing.
17. Moffitt,	M. 2 yrs	Good	Bad hygiene.	6 days	Left apex.	.....	...	...	...	Recov.	.....	Expect-orants.	
18. Mellenk,	M. 3 yrs.	Good	.....	11 days	Both lungs.	Extreme restlessness	...	...	...	Death.	.....	Digitalis, whiskey.	Resolution never occurred
19. Streeper,	M. 3 yrs.	Good	Whooping-cough.	8 days	Both bases.	.....	...	...	104	Death.	.....	Digitalis, whiskey.	Gradual extensions.
20. Ferguson,	M. 3 yrs	Good	Exposure.	5 days	Left base.	.....	...	...	...	Recov.	.....	Nothing.	Signs late in developing.
21. Craighead,	M. 3 yrs.	Good	.....	8 days	Right apex.	.....	180	96	104	Recov.	.....	.....	Resolution was long in becoming completed.
22. Metzler,	M. 3 yrs.	Good	.....	7 days	Right base.	.....	...	...	103	Recov.	.....	.....	Sister sick in bed with pneumonia.
23. Harlay,	F. 3 yrs.	Good	.....	1 day	Left base.	.....	...	...	...	Recov.	.....	.....	Fever and restlessness disappeared after 24 hours; signs persisted.
24. Curry,	F. 3 yrs.	Good	Whooping-cough.	1 week	Left base.	Much bronchitis, cyanosis.	160	80	...	Recov.	.....	Digitalis, carb. am.	Child thought to be dying; stimulants doubled and recovery occurred.
25. Ward,	F. 3 yrs.	Good	.....	6 days	Right apex.	.....	148	54	103	Recov.			
26. Schilling.	M. 3 yrs.	Good	.....	7 days	Right base.	Meningeal signs.	...	...	...	Recov.	.....	.....	Marked strabismus and opisthotonus.
27. Walters,	M. 3 yrs.	Good	.....	4 days	Right base.	Vomiting, delirium.	160	...	105	Death.	Confined.	KBr.	Child unconscious from beginning.
28. S.	F. 2½ yrs.	Good	Cough for several days.	8 days	Left lung.	Convulsions	...	...	104	Recov.	.....	.....	Temperature disappeared by lysis.
29. Norton,	M. 3 yrs.	Good	Cough two weeks.	3 days	Left base.	Dyspnœa.	130	53	105	Recov.	.....	.....	Crisis occurred on third day.
30. Hoffman.	F. 3 yrs.	Good	.....	11 days	Right apex.	Entero-colitis.	...	...	104	Death.	.....	Digitalis	For several days signs of simple entero-colitis.
31. Rosenberger,	M. 3 yrs.	Good	.....	4 days	Right apex	.....	...	...	103	Recov.	.....	.....	Sister sick with pneumonia.
32. W.	F. 3 yrs.	Good	.....	7 days	Right base.	.....	160	69	103	Recov.	.....	.....	Signs did not appear for four days.
33. N.	F. 3 yrs.	Good	.....	10 days	Left base.	Irregular.	...	...	...	Recov.	.....	.....	Fever for several days; a drop in temp. Recovered and signs of consol.
34. Italian,	F. 2 yrs.	Good	No care.	7 days	Right base.	.....	...	...	103	Recov.	.....	.....	On 7th day child brought into office, carried half a mile through rain; no bad effects.
35. Soley,	F. 3 yrs.	Good	.....	7 days	Whole r. lung.	Extreme prostration.	148	...	104	Recov.	.....	Digitalis.	

Name.	Sex and age.	Family history.	Personal history.	Duration.	Seat of lesion.	Special symptoms.	Pulse	Respiration.	Temperature.	Result.	Post-mortem.	Treatment.	Remarks.
36. Shaw,	M. 3 yrs.	Good	Ear disease.	10 days	Right apex.	Meningeal symptoms.	...	...	104	Recov.	.....	KBr, KI, digitalis.	Very rapid respirations; convulsive movements; cyanosis.
37. Gallagher,	F. 3 yrs.	Good	.....	7 days	Right base.	Severe convulsions for three days.	...	...	...	Recov.	.....	.....	Entire recovery without any very severe symptoms.
38. Conway,	M. 3 yrs.	Good	.....	4 days	Right lung.	Convuls'ns just before death.	...	...	107	Death.	.....	Stimulation.	
39. M.	F. 3 yrs.	Good	.....	9 days	Left base.	.....	...	...	105	Recov.	.....	.....	Marked crisis.
40. Brinsinghoffer,	F. 3 yrs.	Good	.....	1 week	Right apex.	.....	...	80	103	Recov.	.....	Digitalis.	
41. Devas,	M. 4 yrs.	Good	.....	1 week	.....	Nephritis.	...	...	...	Recov.	.....	.....	Entire recovery; no signs of Bright's disease at present.
42. Scheetz,	M. 4 yrs.	Good	.....	1 week	Left base.	Marked typhoid symptoms.	...	...	...	Death.	C'nfirm'd diagnosis of pneumonia.		
43. Priest,	F. 4 yrs.	Good	.....	9 days	Right apex.	.....	...	...	...	Recov.	.....	Expectorants.	
44. Bennett,	F. 4 yrs.	Good	.....	.....	Both bases.	Expiratory movements	150	68	104	Recov.	.....	.....	Developed measles while convalescent.
45. Forrest,	F. 4 yrs.	Good	.....	7 days	Right base.	Meningeal symptoms.	...	...	...	Recov.	.....	Stimulation.	
46. L.	F. 4 yrs.	Good	.....	6 days	Right base.	.....	...	...	...	Recov.	.....	.....	Crisis sixth day.
47. A.	F. 4 yrs.	Good	.....	8 days	Left base.	.....	140	40	104	.....	.....		
48. Alvitz,	F. 2¼ yrs.	Good	.....	6 days	Right apex.	Convulsions.	...	...	103	Recov.	.....	.....	No nursing.
49. Carty,	M. 4 yrs.	Good	.....	13 days	Right lung.	.....	128	72	108	Death.	.....	Stimulants.	Disease organ with consol. of apex; temp. fell; this recurred and there was consol. of base.
50. Heller,	F. 4 yrs.	Good	.....	7 days	Left base.	.....	...	...	...	Recov.	.....	.....	Influenza by another M.D.
51. Howard,	M. 4 yrs.	Good	.....	4 days	Left base.	Much pain.	...	...	...	Recov.	.....	Nothing	
52. Schroeder,	F. 4 yrs.	Good	.....	5 days	Left base.	.....	...	...	...	Recov.	.....	Nothing.	
53. Mabel,	F. 5 yrs.	Good	.....	6 days	.....	.....	...	...	...	Recov.	.....	Ice.	Followed by empyema, drainage, and recovery.

54. Clemmens,	F. 5 yrs.	Good	.....	.....	Right base.	.....	...	...	...	Recov.	.....	.....	But little fever.
55. Stoel,	F. 5 yrs.	Good	.....	6 days	Right base.	.....	...	...	...	Recov.	.....	.....	No severe signs.
56. Mackleer,	M. 5 yrs.	Good	.....	8 days	Left apex.	.....	...	...	104	Recov.	.....	Digitalis,	
57. Rapp,	F. 5 yrs.	Good	.....	9 days	Left lung.	.....	132	52	104	Recov.	.....	Digitalis,	
58. Kirkpatrick,	M. 6 yrs.	Good	.....	6 days	Right apex.	Convulsions.	...	...	105	Recov.	.....	KBr.	For several days the right apex was more resonant than left; consolidation occurred rather suddenly
59. G.	M. 6 yrs.	Good	.....	4 days	Left base.	Convulsions.	...	...	104	Recov.			
60. Rosenberger,	F. 6 yrs.	Good	.....	7 days	Left base,	.....	...	...	103	Recov.	.....	Expectorants.	Brother immediately developed pneumonia.
61. Maff,	M. 6 yrs.	Good	.....	4 w'ks	Whole r. lung.	.....	...	...	104	Recov.	.....	Digitalis, strychn.	Whole rt. lung developed a remarkably slow resolution; entire recovery.
62. Hopkins,	F. 6 yrs.	Good	.....	6 days	Right apex.	.....	136	...	103	Recov.	.....	Ice, digitalis.	
63. McCon,	F. 6 yrs.	Good	.....	6 days	Right apex.	. ...	...	...	103	Recov.	.....	Expectorants.	Child out playing when seen ninth day.
64. Noble,	M. 6 yrs.	Good	.....	4 days	Right base.	.....	112	40	104	Recov.	.....	.....	Severe early symptoms.
65. D.	F. 6 yrs.	Good	.....	9 days	Right apex.	.....	160	40	102	Recov.	.....	.....	Signs did not appear until third day.
66. Sloan,	F. 7 yrs.	Good	.....	.....	Right base.	Collateral œdema.	...	...	...	Death.	.....	.....	Child had been ill several days, no attention; death within 24 hours after first visit.
67. Hinkle,	M. 7 yrs.	Good	Measles.	12 days	Left base.	.....	120	48	104	Recov.			
68. Noble.	M. 6 yrs.	Good	Chills.	7 days	Right apex.	Expiratory movements	101	52	105	Recov.	.....	Digitalis.	
69. McMaster,	M. 7 yrs.	Good	.....	4 days	Right base.	.....	...	...	...	Recov.	.....	Expectorants.	Three sick with pneumonia in house at once
70. Priest,	F. 7 yrs.	Good	Nephritis.	4 days	Left base.	.....	...	...	103	Recov.	.....	Digitalis,	Increase of alb. and casts.
71. Metzler,	F. 7 yrs.	Good	... ..	4 days	Right base.	Constant vomiting.	...	...	...	Recov.	.....	.....	Signs unequivocal; brother developed pneumonia in a few days.
72. Breng,	F. 8 yrs.	Good	.....	7 days	Left base.	Pericarditis.	...	...	103	Recov.	.....	.....	Heart lesions developed.
73. Grey,	F. 8 yrs.	Good	.....	6 days	Left base.	.....	140	40	103	Recov.	.....	Expectorants.	Child had no nursing.
74. Pester,	F. 8 yrs.	Good	.....	6 days	Left base.	.....	...	...	104	Recov.	.....	.....	Second attack.
75. C.	F. 9 yrs.	Good	.....	5 days	Right base.	.....	110	5	103	Recov.	.....		

Name.	Sex and age.	Family history.	Personal history.	Duration.	Seat of lesion.	Special symptoms.	Pulse	Respiration.	Temperature.	Result.	Post-mortem.	Treatment.	Remarks.
76. Leflar,	M. 10 yrs.	Good	.....	6 days	Right base.	Herpes.	...	...	101	Recov.	.....	.....	On 3.16, sore-throat. " 3.17, herpes labialis. " 3.18, consolidation. " 3.21, child apparently well, but phys. signs remained.
77. Noble.	M. 12 yrs.	Good	.....	5 days	Right apex.	Delirium.	...	...	..	Recov.			
78. McElhey,	M. 11 yrs.	Good	.....	4 days	Right apex.	Sudden onset.	...	...	...	Recov.	.....	Whiskey, digitalis.	
79. Bisbing,	F. 13 yrs.	Good	.....	8 days	Right base.	.....	...	...	103	Recov.	.....	.....	Signs appeared late.
80. Bostic,	M. 13 yrs.	Good	.....	8 days	Left base.	.....	112	56	104	Recov.	.....		
81. Norton,	F. 15 yrs.	Good	.....	5 days	Whole r. lung.	.....	124	44	102	Recov.	.....	.....	Mother immediately developed pneumonia.
82. Van,	F. 20 yrs.	Good	.....	7 days	Left base.	.....	120	...	104	Recov.	... .	.....	Lysis.
83. Graolff,	M. 13 yrs.	Good	.....	5 days	Left base.	.....	...	...	105	Recov.	.....	Expectorants.	
84. Cahill,	F. 20 yrs.	Good	.....	7 days	Base.	.....	...	...	...	Recov.	.....	.....	Found her walking about with consolidated base.
85. McCarty,	M. 21 yrs.	Good	.....	1 w'k	Right base.	.....	...	...	101	Recov.			
86. Fye,	M. 21 yrs.	Good	Drinker.	9 days	Right base.	Extreme dyspnœa, low temp.	...	...	102	Recov.			
87. Slater,	F. 21 yrs.	Good	.....	10 days	Whole r. lung.	Nephritis.	...	...	...	Recov.	.....	Ice, digitalis.	Brother, pneumonia in same house.
88. Jones,	F. 21 yrs.	Good	.....	4 days	Base.	.....	...	...	...	Recov.	... .	.....	Girl down stairs fourth day; no relapse.
89. Collins,	M. 21 yrs.	Good	.....	4 days	Right base.	.....	...	...	103	Recov.	.....	.....	Rusty sputum; all symptoms developed by fourth day.
90. Fisher,	F. 22 yrs.	Good	.....	15 days	Whole r. lung.	.....	...	...	103	Recov.	.....	.....	Signs of dysentery first.
91. W.	M. 24 yrs.	Good	.....	4 days	Left base.	Pain.	...	12	104	Recov.	.....	.....	Crisis fourth day.
92. Batzell,	F. 24 yrs.	Good	.....	7 days	Left base.	.....	...	...	103	Recov.			
93. Gobers,	M. 26 yrs.	Good	.....	8 days	Right base.	.....	...	...	...	Recov.	.....	.....	Diagnosis not made out until crisis.

94. Laurence,	M. 27 yrs.	Good	.....	9 days	Right base.	Nephritis.	...	...	104	Recov.	.....	.....	No special treatment; man ill; nephritis cleared up.
95. Kelly,	M. 28 yrs.	Good	.....	9 days	Base.	Pain.	100	40	104	Recov.	.....	.....	Man in street on tenth day.
96. Hune,	M. 26 yrs.	Good	Influenza; drinker.	7 days	Right base.	.....	...	...	105	Death.			
97. Bernard,	F. 24 yrs.	Good	.....	7 davs	Right lung.	Pain.	...	...	...	Recov.	.....	.....	Signs later.
98. Foster,	F. 30 yrs.	Good	.....	.....	Left base.	.....	...	...	104	Recov.	.....	Digitalis,	
99. Wolfmuller,	F. 80 yrs.	Good	Fat.	4 days	Right base.	.....	...	...	104	Death.	.....	.....	No resistance.
100. Scott,	M. 23 yrs.	Good	.....	6 days	Left base.	.....	...	...	108	Recov.	.....	.....	No treatment except cotton and rest.
101. Wager,	M. 22 yrs.	Good	.....	10 days	.....	.....	...	...	104	Recov.	.....	.....	Delayed resolution; final complete recovery.
102. Libbald,	F. 23 yrs.	Good	.....	9 days	Whole r. lung	.....	...	...	104	Recov.	.....	.....	Crisis.
103. Jones,	M. 35 yrs.	Good	.....	10 days	Left base	.....	...	...	...	Recov.	.....	Expectorants.	
104. Johns,	F. 37 yrs.	Good	Pregnant.	5idays	Both lungs.	.....	...	104	...	Death.	.....	Poultice, digitalis.	Death 24 hours after premature birth of child.
105. Kelly,	F. 40 yrs.	Good	Pregnant.	5 days	Both lungs.	.....	...	104	...	Death.	.....	Ice.	Died 24 hours after premature birth of child.
106. Harris,	M. 33 yrs.	Good	Drinker.	7 days	Left base.	.....	...	102.5	...	Recov.	.....	Ice, digitalis.	
107. Stanley,	F. 37 yrs.	Good	Heart disease.	7 days	Left base.	.....	...	104	...	Death.	.....	Ice.	Sudden collapse.
108. Walton,	M. 40 yrs.	Good	Exposure.	7 days	Right base.	.....	...	...	...	Recov.	.....	Digitalis.	
109. Norton,	F. 40 yrs.	Good	.....	9 days	L. & r. base.	.....	...	...	...	Recov.	.....	Digitalis.	Daughter contracted pneumonia same month.
110. Patton,	F. 40 yrs.	Good	Woman pregnant.	14 days	.....	.....	...	...	...	Recov.	.....	.....	Aborted when temperature normal.
111. Wier,	M. 42 yrs.	Good	Tuberculous knee.	1 week	Left base.	Bronchitis.	...	101	...	Recov.	.....	.....	Much capillary bronchitis.
112. John,	M. 42 yrs.	Good	.....	1 week	Right base.	.....	...	103	...	Recov.			
113. Entwill,	M. 44 yrs.	Good	Tuberculous spine.	10 days	Left apex.	.....	...	104	...	Recov.	.....	.....	Signs severe development from apex, but patient well for four years.
114. McGuigan,	F. 42 yrs.	Good	Feeble.	8 days	Left base.	.....	...	...	104	Recov.	....	Ice, digitalis.	
115. McMaster,	M. 47 yrs.	Good	.....	9 days	Whole r. lung, l. base.	.....	...	70	102	Recov.	.....	Ice, strychn.	The respirations were 70 for 24 hours,
116. Thompson,	M. 42 yrs.	Good	.....	8 days	.....	.....	...	...	103	Recov.	.....	Ice, digitalis.	

Name.	Sex and age.	Family history.	Personal history.	Duration.	Seat of lesion.	Special symptoms.	Pulse	Respiration.	Temperature.	Result.	Post-mortem.	Treatment.	Remarks.
117. Thompson,	M. 46 yrs.	Good	Drinker.	4 days	Both lungs.	.....	...	...	...	Death.	.....	Ice.	Collapse.
118. Philips,	M. 45 yrs.	Good	Drinker.	4 days	Both lungs.	Laryngitis.	...	...	104	Death.	.....	Ice.	Much pain.
119. Osborne,	M. 45 yrs.	Good	.....	9 days	Right base.	.....	...	...	101	Recov.			
120. Schröder,	F. 50 yrs.	Good	.....	7 days	Left base.	.....	...	...	...	Recov.	.....	Hypo. strych.	
121. Martin,	M. 50 yrs.	Good	.....	8 days	Right base.	.....	92	...	104	Recov.	.....	Digitalis,	Very ill, but treatment always full.
122. Heffner,	F. 50 yrs.	Good	.....	.....	Right base.	.....	...	...	...	Recov.	.....	Digitalis, whisky.	
123. Cole,	F. 50 yrs.	Good	.....	6 days	Left base.	.....	...	...	...	Death.	.....	.....	Told by a "friend' she would die; collapsed.
124. Rice,	F. 55 yrs.	Good	Atheromatous.	5 days	Right base	Vomiting.	...	...	101.5	Death.	.....	.....	Sudden collapse.
125. Haggerty,	F. 56 yrs.	Good	Heart-lesion.	6 days	Left base.	.....	...	...	...	Death.	.....	.....	Sudden collapse after crisis had occurred.
126. Magill,	F. 56 yrs.	Good	Heart-disease.	7 days	Whole r. lung.	Pain.	...	...	103	Recov.	.....	.....	Woman living ten years after attack.
127. Gilton,	F. 55 yrs.	Good	Diabetes mellitus.	7 days	Right base.	.....	108	28	102	Recov.	.....		
128. James,	F. 58 yrs.	Good	.....	7 days	Right base.	.....	...	...	104	Recov.	.....	.....	Crisis.
129. Taylor,	F. 60 yrs.	Good	Weak.	7 days	Right base.	.....	108	28	102	Recov.	.....	Cotton, digitalis	Never appeared very ill (influenza).
130. Schutz,	M. 59 yrs.	Good	Drinker.	9 days	Whole r. lung.	.....	...	...	...	Death.	.....	Ice, strych., hypodermic.	
131. Shannon,	F. 60 yrs.	Good	Drinker.	.....	Whole l. lung.	.....	1	...	100	Recov.	.....	Digitalis.	Never had a bad symptom.
132. Bert,	F. 60 yrs.	Good	.....	9 days	Right apex.	.....	...	...	103	Recov.	....	Expectorants.	
133. Jones,	F. 72 yrs.	Good	Heart-disease.	7 days	Whole r. lung.	.....	93	48	103	Recov.	.....	Digitalis.	
134. Reamohart,	F. 86 yrs.	Good	Heart-disease.	.....	Whole r. base.	.....	...	...	.100	Recov.	....	Digitalis.	Notwithstanding severe cardiac symptoms patient never had a bad symptom from consol. which cleared up, and she lived two months.

Its value may be well illustrated by Case 114. A man, aged forty-seven years, with double pneumonia, moderate fever, went along well until the sixth day; then the heart became rapid, and respirations the most rapid I have ever seen; he breathed 70 per minute from 7 A.M. to 12 midnight. For some unknown reason strychnine had not been used, oxygen, digitalis, and whiskey had been given to their fullest extent, without relief. At 8 P.M. he was breathing 70 per minute; a hypodermic of one-twentieth grain of strychnine was given with some relief. It was repeated at 10 and at 12; by 2 A.M. respirations were 50 per minute, and from that time on convalescence was rapid.

Digitalis and whiskey, I believe, are valuable, and many of my cases seem to prove it; but these drugs are much more unmanageable in a crisis than strychnine used hypodermically.

Venesection I have never tried. One case of double pneumonia seemed to demand it, but it was refused. This is the only case in which there seemed to be any call for the remedy. Aconite and veratrum viride I have never used, being afraid of their overaction.

External Applications. In all of my first cases a jacket poultice was used. It was troublesome, uncleanly, and uncomfortable, and was soon discontinued, except in certain cases. Where there is much bronchitis and consequent embarrassment of breathing the application of a poultice which envelops the whole chest is followed by such immediate and striking relief that it cannot be a coincidence. Where pain is great a small hot poultice over the affected area will relieve.

I still use cotton-jackets, but I must confess with no special good effects, except to quiet the minds of the patient and friends I believe they do no harm. I have carefully watched for a rise of temperature following their use, but failed to discover any. A case is now under treatment which had a temperature of 104° on the first visit. A cotton-jacket was applied, and this morning the temperature is 100.5°.

Cold. A cold bath when the temperature is high gives the greatest relief, and a delirious patient will frequently go gently to sleep under its influence. I believe case 37 would have been saved by its application; he died in a convulsion, with temperature of 107°.

Local applications of ice to the affected side are theoretically correct. They certainly relieve pain, but my own experience with them has been fatal. I still use them where there is a tendency to high tem-

perature. I believe such articles as have recently appeared, where isolated cases have been received from all over the country, "ice has been used and recovery occurred," is the usual record, are most mischievous. Cases can and do recover with absolutely no treatment. A single case proves nothing.

The pain, which is frequently the most annoying symptom, can best be relieved by ice or poultice. Externally, by cups or by opiates.

The temperature, if above 103°, is kept down by cold bathing; but, as a rule, except for the discomfort it causes, the temperature may be left to itself.

PERICARDITIS: SOME POINTS IN ITS DIAGNOSIS AND TREATMENT.

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THERE is perhaps no disease with which we are so well acquainted more frequently overlooked during life than pericarditis. Among the reasons for this failure in diagnosis may be mentioned, first, the fact that pericarditis, like the inflammation of the other serous membranes, is commonly and perhaps invariably secondary. Rheumatism is the most frequent primary disease; but in rheumatism the endocardium is attacked even more frequently than the pericardium, and thus two possibilities of error are afforded. In the first place, it is in some cases not easy, unless after repeated careful examination, to determine positively the endo- or exocardial origin of adventitious sounds; and, in the second place, both membranes may be simultaneously attacked, while the auscultatory sounds of the endocarditis wholly or very largely mask those of the pericarditis. Again, it is notorious that, especially in children, the rheumatic poison may be manifested so slightly in the joints that it is not thought worth while to call in the doctor, who thus misses a chance of noting the commencement of an inflammation resulting later in adherent pericardium or a damaged valve. While many other joint-diseases and infections may be complicated by pericarditis, in none, save pneumonia, is it so common as to lead us to be specially on the watch for it. Tuberculosis may attack the pericardium either alone, just as it may attack the pleura; or together with other serous membranes, as well as parenchymatous organs in varying degree, as in the acute miliary form; or, third, as an extension from the contiguous lung or pleura in chronic pulmonary consumption. Such extension seems to be rare, considering the very large number of cases of fatal phthisis. Except in cases where the tuberculosis is confined

to the pericardium, and is then accompanied by considerable effusion or more or less pronounced local symptoms, the condition of the serous sac is liable to be overlooked. In pneumonia and other forms of lung inflammation, and also in pleurisy complicated by pericarditis, it may easily be impossible even for the most skilled and careful observer, owing to the anatomical relations of these organs, to detect and differentiate the pericardial inflammation.

The frequent association of pneumonia and pericarditis, as well as the latency of the latter, has forced itself upon my attention of late. Of 57 cases of pneumonia under my care in the hospital during the past three years 20 have come to autopsy. In 13 of these pericarditis was found. In 5 of the 13 pericarditis was detected during life. In the other 8 it was carefully sought for, and the absence of its signs was recorded. In 7 of the 13 cases the pneumonia was right-, in 6 left-sided. This experience differs widely from that of Osler, who found pericarditis in only 5 of 100 autopsies of those dying from pneumonia in the Montreal General Hospital.

In a similar way hydropericardium, with or without inflammation of the sac, in cases of nephritis and cardiac insufficiency may be quite masked by hydrothorax, ascites, passive congestion of the liver and other results of hydræmia and stasis.

Symptoms, again, are not to be relied upon as suggestive of pericarditis or in any way distinctively diagnostic. The primary disease may be so severe as to render the additional load almost imperceptible to the observer. Pain in the cardiac area is very frequently absent, often slight, most apt to be marked in the relatively vigorous with mild primary disease. It is, perhaps, a fair general statement that the less severe the original disease the more likely are symptoms suggestive of secondary pericarditis to be present. Ordinarily there is nothing about the facies, position, breathing or pulse essentially different from what may be seen in many other forms of intrathoracic disease. The temperature-range, as in other serous sac inflammations, has no distinctive peculiarities.

Diagnosis must, then, rest mainly on physical signs, but these may be entirely absent. I have deeply stamped in my memory the case of a physician's wife, some years ago. Double dry pleurisy was present, and, believing that pericarditis must be also present, twice daily for nearly two weeks I examined the præcordia with the greatest care

without ever succeeding in detecting any friction which I could refer to the pericardium. At the autopsy the pericardial surfaces were uniformly united by delicate and recent adhesions. Friction, again, is proverbially often evanescent, and may come and go between examinations which may be separated by too long an interval, the first having given negative results, and no new local or circulatory symptom arising. It has happened to me more than once, the last time within a few months, to order a patient with well-marked pericardial friction sent to my clinic at the amphitheatre the next morning, that students might have the opportunity of listening to it, and then to find that the friction had disappeared entirely. Another trap which is set for us is the pleuro-pericardial friction. If there is no other evidence of a process in the lung with which pleurisy is apt to be associated, and no other evidence of pleurisy than friction within the præcordial limits, the chances are in favor of the pericardial origin of the friction, especially in the rheumatic cases. Conversely, with other evidences of pleurisy or of a cause for it, a friction in the above area is probably pleural; but we have all encountered cases where a double friction accompanying the cardiac movements and persisting during cessation of respiration has subsequently proved to have originated solely in the pleura bordering on the heart.

Another pitfall is, the lungs and pleura being beyond suspicion, the association of endo- and pericarditis of undoubted rheumatic origin, if you like. Two recent personal cases illustrate this point:

CASE I.—A boy of six was seen with Drs. Miles and Coggeshall, acutely and very seriously ill with symptoms of defective circulation; endocarditis was apparently unquestionable. During both the examination and subsequent discussion of the case the possibility of considerable pericardial effusion occupied the foremost place. The enlargement of the area of cardiac dulness was quite moderate; gentle percussion was resonant in the fifth right interspace (Rotch); the dulness did not seem to extend to the left beyond the impulse; the præcordia was not prominent, and I believed that an attempt to tap the pericardium would pierce the ventricle, and thereby hasten death. The end came in about twenty-four hours. There was no autopsy, but the undertaker states that from the incision which he made near the heart for embalming purposes nearly a quart of clear, yellow fluid escaped. My inevitable conclusion from this is that death was immediately due to a large pericardial effusion, the removal of which might have saved the child's life, but which had not manifested its presence by signs characteristic of such condition though the possibility of its presence was carefully weighed.

CASE II.—A few weeks later a boy of eleven was admitted to my ward with a doubtful history of mild articular inflammation, a systolic apex-souffle, and a double murmur below the base on the left so soft and regular as to suggest an endocardial origin, though pressure with the stethoscope increased its intensity. A few days later the double murmur changed its character, and I was satisfied that it was due to pericarditis (Case VIII.); in short, we had a rheumatic endo-pericarditis. Soon after, the pulse rose to 160 and was paradoxical; orthopnœa and præcordial pain were present, and the urine fell in quantity. Coincidently the area of dulness increased and extended to the left of the impulse. I pushed a good-sized trocar and canula into the fifth space an inch beyond the nipple just inside the line of flatness. That I entered the pericardium was proved by getting about two drachms of serous fluid. The end of the canula moved freely, as if in a cavity; adhesions were not felt breaking; perviousness of the canula was proved by reinsertion of the trocar. The cardiac movements communicated to the canula were alike visible and palpable, but no more fluid could I get. From this time the boy began to improve, morphia and alcohol being continued, and a week later all signs of pericarditis had disappeared. Here I was either mistaken as to the amount of effusion or it was trabeculated something like a variolous vesicle. The latter possibility was suggested to me by a previous case (Case I.) in which I could not extract as much fluid as the signs would warrant me in expecting to get, though I tapped in several places.

These cases show that I at least find it sometimes difficult, though trying to exercise due diligence, to determine the presence or degree of pericardial effusion, especially when endocarditis is also present, though the lungs and pleuræ are clear.

Dry pericarditis is not to be diagnosticated with certainty in the absence of friction, the possible pleural origin of which is always to be borne in mine. Practically, perhaps, it is not of much consequence, as obliteration of the sac is the worst sequence.

A small effusion may be suspected, but is not to made out with certainty. What the least amount of fluid that can be detected may be, I cannot state. I suspect that it is not fixed, but varies with different patients as well as with different observers. The practically important thing is to be able to recognize a considerable or large effusion, to decide rightly whether tapping is necessary and to practise it successfully. Since I published a little book on *Auscultation and Percussion*[1] I have had more experience with pericardial effusion than in all the rest of my professional life, and my belief as to the shape of the dul-

[1] G. S. Davis, 1890.

ness produced by effusion differs now from that of most writers on the subject whose views I then accepted. I do not find, namely, that the dulness of the large effusion is either pear-shaped or pyramidal. To my percussion the area of dulness is simply that of the normal heart equally extended in all directions; therefore, of course, it is also that of a symmetrically enlarged heart, though the latter can seldom if ever produce so large a dull area. It is always my attempt in cardiac percussion to map out the limits of the heart itself, disregarding the smaller area, that of cardiac flatness so-called, within which the pericardium uncovered by lung comes immediately in contact with the chest-wall. By inserting needles along the line of dulness, as determined during life or just before the autopsy, in a number of cases, and then opening the body, I have satisfied myself that substantial accuracy is thus possible. The pyramidal and pyriform-shaped areas may result from aiming to mark out flatness rather than dulness, a procedure which the very gentle percussion required in this work renders more difficult to me than the plan which I have pursued. In several cases of large effusion I have noticed dulness below the left clavicle as compared with the other side, but have never been able to make out any percussion-changes in the back which I could connect with a distended condition of the pericardial sac. The impulse of the heart may or may not be visible, palpable, or both. In the cases in which it is accessible to sight or touch distinct extension of the dulness to the left of such impulse has seemed to me a very important physical sign of effusion within the sac. If no impulse can be seen or felt, the maximum intensity of the first sound must serve as the best indication of the seat of the apex. Change in the percussion sounds, upward or laterally, with change in the position of the patient, is very valuable if it can be distinctly made out. Such change was noted in three out of four of my recent cases. Silence on this point in the others tends to show that the sign was not specially studied. Prominence of the præcordia is, I am sure, not frequent, and no important conclusions should be based on its absence, which I have noted even in a young subject. The lungs offer less resistance than the chest-wall and may both retract away from the distended pericardium. Moreover, the limits of possible effusion are more definite in the case of the pericardium than in the case of the pleura. Paradoxical pulse was noted in five out of eight cases. Effusion was large or considerable in all

where it was present; but the value of this sign is lessened by the fact that it may be found also in other conditions, though, perhaps, less constantly. Repeated and sudden collapse was noted in six cases, and therefore seems to be a sign worth mention. In none of my cases was aphonia, dysphagia, or irritative cough a noteworthy symptom.

The diagnosis of uncomplicated considerable pericardial effusion should ordinarily present no great difficulty, especially if the observer has had the opportunity of watching the case and noting the development of the symptoms and physical signs. A weak and dilated heart, an encapsulated pleural effusion, and possibly a mediastinal new-growth are the conditions involving most liability to error. The difficulties of diagnosis in complicated cases have been already dwelt upon sufficiently in a communication which makes no pretence of exhausting the subject, but is rather a record of personal experience.

TREATMENT.—In a general way I must confess my skepticism as to the value of therapeutic measures other than rest as materially modifying the formation or promoting the absorption of pericardial effusion. I have seen effusion increase in spite of remedies, and I have seen it rapidly diminish without remedies. Morphine should be used freely if pain demands it. Alcohol and digitalis should be given if the state of the circulation seems to call for them. Blisters I never use, as my faith in their efficacy is small, and I know they interfere with close study of the case, and may interfere with necessary puncture. The ice-bag I have applied when it was grateful to the patient. I relate annually to my students a story of Sir William Gull told me by Dr. Pye-Smith. At a consultation Gull detected a pericarditis which had been overlooked by the attending physician, who was perhaps unduly apologetic for his oversight. After hearing him out Sir William remarked: "Oh, it is all right. Perhaps it is just as well you did not find it, for if you had you might have treated it." It is my belief that he meant to enounce a general principle rather than to express doubts as to the skill or wisdom of the individual. To tap or not to tap, that is the practical question to my mind, and unless we are quite sure of our diagnosis of a large effusion the question may be a very nice one. Whatever may be our attitude to-morrow, to-day we cannot regard puncture of the heart as an innocent procedure, and we cannot bring ourselves to interfere with the pericardial as freely as with the pleural cavity. The consequences of

an error are liable to be too serious according to our present knowledge; and yet the fact that I have in seven cases attempted to tap the pericardium, in six successfully, is proof, I think, that I am not more timid in this respect than most people. I believe I have saved at least two lives by tapping. In Case II. the fluid finally ceased to reaccumulate. In Case VII. tapping proved the necessity for free incision. I have never regretted having tapped. I have reproached myself for not having tapped.

There is a double danger in every large pericardial effusion; that of sudden and that of gradual failure of the heart, embarrassed as it is. The frequency of sudden collapse in my cases has been already alluded to. Fortunately in none was it fatal; but the withdrawal of a relatively small amount of fluid may obviate this tendency. Moreover, it has seemed to me, alike in pericardial and in pleural effusion, that absorption sometimes follows the removal of even a small amount so rapidly as to suggest a causal connection. Of course, absolute proof of this is hard to obtain, and perhaps I should exercise fully as much skepticism here as with regard to drugs, blisters, and the like. No hard-and-fast rule can be laid down with reference to when to tap. Each case must be determined on its merits; but if the diagnosis of considerable effusion seems sure, if the breathing and circulation show danger signs, and if the patient be not under close supervision of a competent assistant, I believe it is safer to puncture. If the case is uncomplicated or largely so—that is to say, if it be only the effusion which seems to threaten life—interference is more strongly indicated than if the effusion be merely a single factor, as in Case IV., where malignant endocarditis was strongly suspected. If interference is decided upon, of course, cleanliness of hands, skin, and instrument must be ensured. Personally, I prefer a moderate-sized trocar and canula attached to the aspirator with a side switch.

A smooth canula can be moved freely in all directions within the sac if adhesions or other cause impede the flow, and one feels no nervousness in coming in contact with the moving heart. Repeatedly I have felt the motions with the utmost distinctness, and have indeed sought them when the results were scanty.

The Point of Election. The points advised as most suitable for puncture by most writers group themselves in the superficial cardiac space, the small triangular area where the pericardium is not covered

by lung; that is, the fourth and fifth left interspaces, either at the sternal border or an inch from it, are mentioned by all authorities. Rotch has suggested the fifth right interspace at the sternal border, basing on his cacao-butter injections in the cadaver the opinion that the dilated heart never extends into this space, and that puncture there is consequently safe. The left costo-xiphoid angle, the instrument being thrust upward and somewhat backward, is also recommended for safety. Here I have punctured once only, and then after death—Case IV. The ease with which I withdrew a pint of fluid inclines me to try this point again, and during life, if occasion offers. This inclination is strengthened by preceding several autopsies recently by puncture in this spot. The liver or peritoneum may be wounded in reaching the normal pericardium at this point; but this danger must be small when the pericardium is distended with fluid.

The fact that the line of dulness extends to the left of the impulse—for the probable reason that the fluid seeks the lower and lateral portions of the sac, which, moreover, are more distensible—first led me to try tapping just inside the outer left limit of the line of dulness, and it is here that I have made my most productive punctures, withdrawing once thirty-six ounces; again, in the same case (II.), twenty-four and sixteen ounces; and in another case (VII.) sixteen ounces. I must confess I feel less nervous about thrusting a sharp instrument in so far to the left than directly over the heart. The lung ought to be wounded by puncture so far to the left. This has not seemed to occur in any of my cases, though in Case VII. the incision was made to the left of the nipple and opened the left pleural cavity, producing pneumothorax and collapse of the lung, and probably causing the subsequent empyema. My colleague, Dr. Cutler, agreed with me in the opinion, which was later shown to have been erroneous, that the pleura was probably adherent at this point. This belief and the fact that I had already reached the fluid here, led us to advise it as the point of incision. The case has been reported in full with critical remarks by Dr. Porter, who has since made many careful dissections which show that the fifth left interspace at the sternal border is the point of election for incision. This case is, I believe, the only one which has ever been treated by incision in the Massachusetts General Hospital.

Twice I have punctured in the fourth right space near the sternum,

without getting fluid in either case. In one of these puncture in the fifth left was productive, in the other it also was dry. Very recently my colleague, Dr. Vickery, drew three and one-half ounces from the pericardium through the fourth right space. The patient, who had also pneumonia, died that night, and the autopsy showed about a pint of fluid still in the pericardium.

The following table shows the seat and result of my punctures:

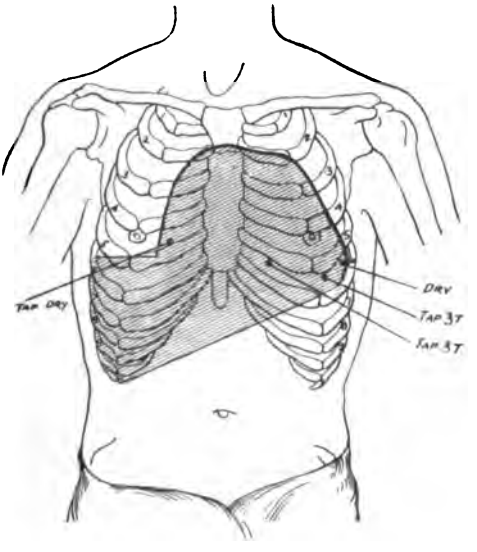
Fourth left . . .	once	fluid.
Fifth left	nine times	seven times fluid, twice dry.
Sixth left . . .	twice	fluid.
Fourth right . . .	twice	dry.
Left costo-xiphoid angle	once, post mortem,	fluid.

CASE I.—Female, aged twenty-four years, single; entered the hospital January 19, 1891, with acute polyarticular rheumatism.

January 23. Pericardial friction; rising temperature and pulse.

28*th*. Chest as in diagram. (Fig. 1.)

FIG. 1.



Tapped in fifth left interspace, three inches from median line. One ounce of bloody serum obtained; heart felt on canula.

Tapped again in fourth right space, two and one-half inches from median line; dry tap.

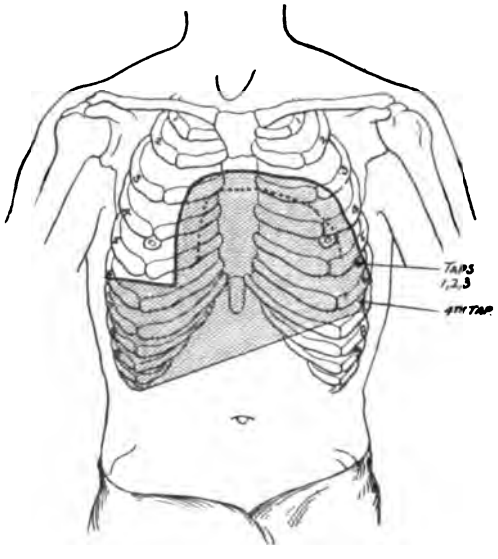
31*st*. Paradoxical pulse. Tapped in fifth left space, four and one-half inches from median line; half an ounce of bloody serum. Next day tapped in same space six and one-quarter inches from the median line; dry tap.

April 12. Discharged well.

CASE II.—Male, colored, aged forty-seven years; entered the hospital on October 26, 1892. Had suffered from weakness and dyspnœa for eight weeks, but had worked in a damp place until entrance. Examination showed pericardial friction with muffled sounds at the apex.

November 19. Steadily losing flesh and strength, but without special symptoms till to-day, when sudden, gasping respiration, weak and almost imperceptible pulse, and fainting. Area of dulness as in diagram. (Fig. 2.)

FIG. 2.



Tapped in fifth left space, one inch outside of nipple, removing twenty-four ounces of serous fluid, containing tubercle bacilli and also the "bacillus pyocyaneus pericarditidis," described by Ernst in the *Transactions* of this Association, 1893, p. 135. Great relief; heart felt on canula.

26*th*. Tapped for same symptoms as before; one pint.

December 17. Tapped for same symptoms as before; thirty-six ounces.

Both these taps were in the same place as the first.

March 5, 1893. Tapped in the sixth left space, one and one-half inches beyond the nipple; one pint; paradoxical pulse.

12*th*. Eloped from the hospital and could not be traced.

CASE III.—Female, aged twenty-four years; entered the hospital January 4, 1893, with præcordial and polyarticular pains, orthopnœa, and gasping,

painful respiration. Dulness beneath left clavicle, and cardiac dulness as in diagram. (Fig. 3.)

FIG. 3.

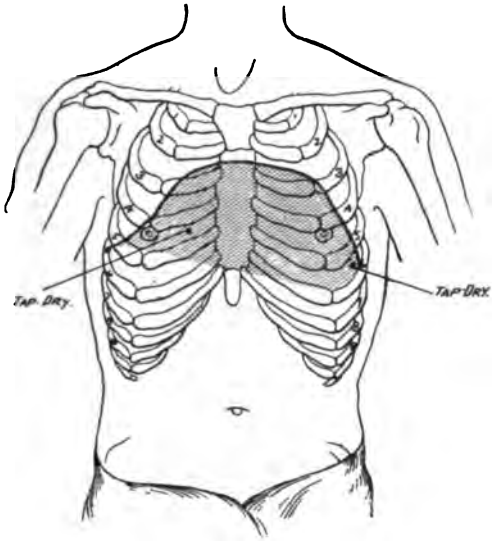
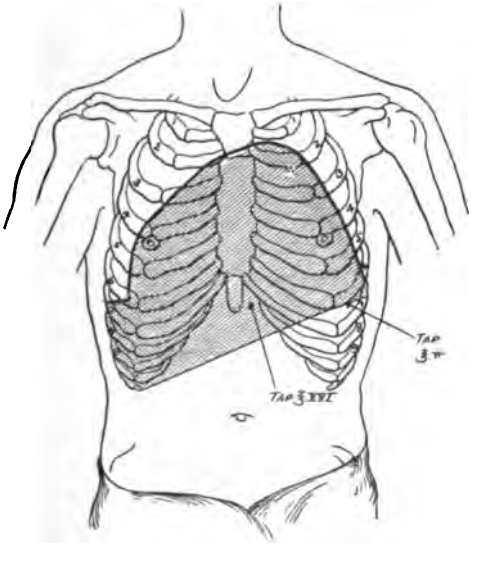


FIG. 4.



The same day, on account of sudden cyanosis and weak and rapid pulse (160), tapped in fourth right and fifth left spaces; both dry; heart felt on canula.

January 7. Died; no autopsy.

CASE IV.—Male, aged about seventeen years; entered on January 5, 1894, after six weeks of polyarticular rheumatism and cardiac symptoms for three weeks. A harsh, systolic murmur over the whole cardiac area.

February 8. Pericardial friction.

17*th*. Dulness as in diagram. (Fig. 4.)

Sudden cyanosis and collapse. Tapped in sixth left space, one and one-half inches outside the left nipple, and two ounces of bloody serum obtained.

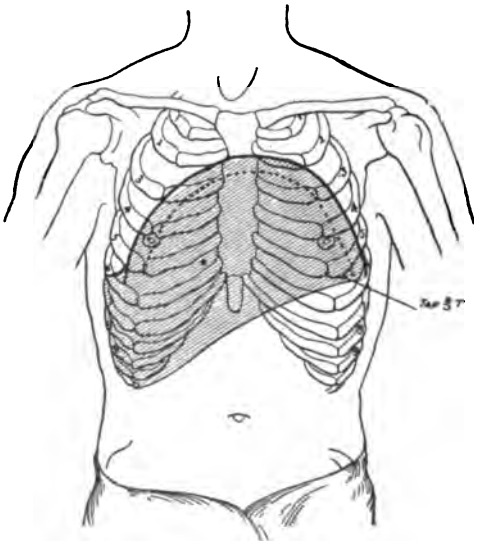
19*th*. Died. No autopsy was permitted, but I tapped after death at the left costo-ziphoid angle, obtaining a pint of serum.

Whether in this case the puncture during life was too far to the left, or whether the effusion increased between that time and death, we have no certain means of knowing. The former seems more probable.

CASE V.—Male, aged six years; entered February 17, 1894, with a history of fever, weakness, dyspnœa, and pain in the chest for ten days. Leucocytes, 18,000.

February 19. Pericardial friction.

FIG. 5.



21*st*. Dulness as in diagram, shifting with change of position. (Fig. 5.)

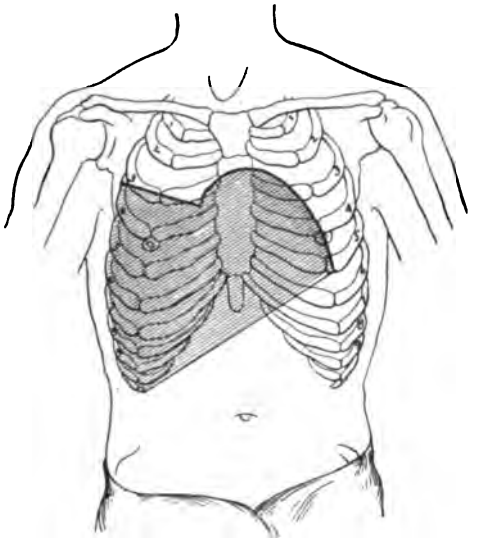
26*th*. Sudden cyanosis and collapse. Tapped in fifth left space, near sternum; one ounce of serum. Died the same day; no autopsy.

CASE VI.—Male, aged forty-seven years; entered April 2, 1895, suffering for four days with pain in various parts of the chest, depending somewhat on position. Cyanosis, labored breathing. Friction, apparently pleural,

over fourth and fifth left costal cartilages; no distinctly pericardial friction. Paradoxical pulse; delirium.

April 5. Area of cardiac dulness has steadily increased, and is now as in diagram. (Fig. 6.)

FIG. 6.



Died the same night. Autopsy: a pint and a half of sero-fibrinous fluid in the pericardium and one pint in the right pleural cavity.

In this case the pericardium ought to have been tapped, perhaps saving life.

CASE VII.[1]—E. C., my junior interne in the hospital, aged twenty-six years, was taken acutely ill October 23, 1895, with pneumonia of the right lower lobe.

October 28. Dry pericarditis. Effusion soon followed, seemed to diminish, but returned and increased.

November 22. The pneumonia having cleared, the condition was critical, the pulse paradoxical, the præcordial dulness as in diagram. (Fig. 7.)

After consultation with Dr. Cutler, tapped in fifth left space, one and one-half inches outside of the left nipple, removing a pint of sero-purulent fluid, containing pneumococci in pure culture. Marked relief.

November 24. The fluid was evidently larger in amount than ever, and the pericardium was incised under ether by Dr. Porter, the cut being made just within the point of puncture. An amount of fluid estimated at a quart escaped; the left pleura was opened; improvement in the pulse and loss of the paradoxical character was almost instantaneous.

[1] For full report of this case, see Boston Medical and Surgical Journal, May 6, 1897, p. 438.

December 4 *and* 24. About six ounces of somewhat turbid fluid were taken from the left pleura. Cheyne-Stokes respiration was present for days.

FIG. 7.

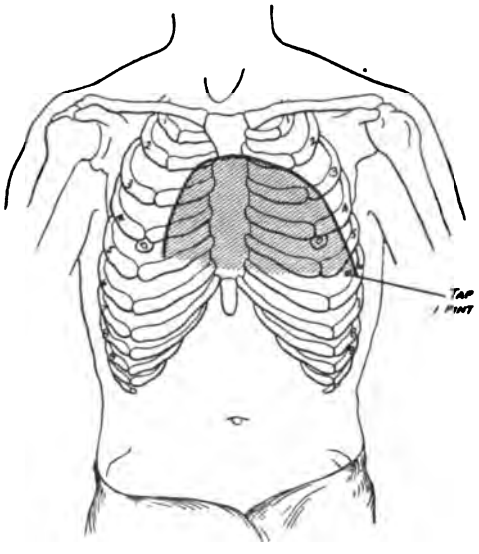
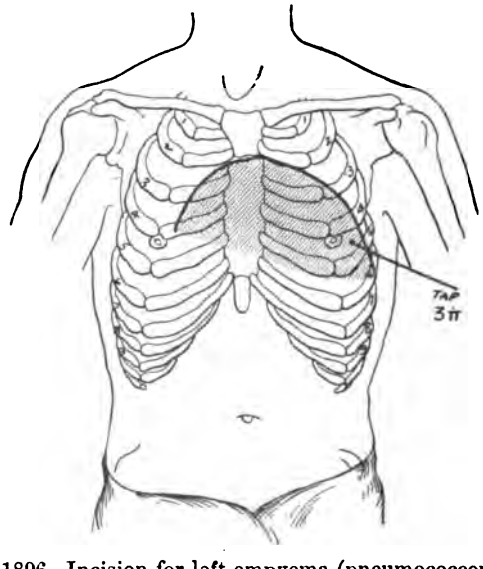


FIG. 8.



January 23, 1896. Incision for left empyema (pneumococcous), with escape of a quart.

February 7. Erysipelas of the whole back, neck, and shoulders.

March 10. Pus was let out of the old pericardial scar and of glands in the left axilla. Pneumococci.

April 27. Discharged from hospital. Recovery of strength has been steady, though gradual. He is now in Europe, and is looking forward to resuming his studies in the autumn.

CASE VIII.—Male, aged eleven years; entered March 1, 1897, with subacute rheumatism, mitral regurgitation, and a pericardial friction.

March 5. Pulse weak and rapid; præcordial pain and dyspnœa; paradoxical pulse. Tapped in fourth left space, just outside the nipple, and two drachms of serous fluid withdrawn. Dulness as in diagram. (Fig. 8.)

24th. Area of dulness much smaller. Symptoms abating.

April 1. Discharged well.

DISCUSSION.

DR. JAMES T. WHITTAKER: During a discussion on the subject of pericarditis in our Academy of Medicine I took occasion once to speak of the rarity of recognition of the disease, and this statement, though disputed, met with singular confirmation from one of the pathologists present in the remark that every one of the five cases which had occurred during his service in one of our hospitals had been recognized only on the post-mortem table. The symptoms—anxiety, pain, palpitation, dyspnœa—are often so obscure or but little marked as to make the diagnosis difficult, and the friction-sound is often quite transitory. And not only this: it is sometimes, notwithstanding all the rules laid down, difficult to differentiate from the murmurs of endocarditis. Of course, any kind of sound over the right heart is more or less suspicious of pericarditis. Moreover, it may be remembered that the friction-sound is quite circumscribed; as Jaccoud said, *Il naît et meurt sur place*, whereas the murmurs of endocarditis are propagated.

After effusion has taken place the diagnosis becomes easier, and the outlines of the pericardium may be usually distinctly distinguished. In making an examination by percussion, after having auscultated the heart, I once made the accidental observation that the sounds of percussion could be appreciated with much greater clearness while the stethoscope was still hanging in the ears. I do not refer here to the auscultatory percussion which has been practised for a long time, and which is done by allowing the stethoscope to rest upon the surface. I do not think this examination is satisfactory, as the instrument wabbles about and produces confused sounds in the ears. In the examination of which I speak the stethoscope dangles over and does not touch the body of the patient. The patient is, of course, recumbent, and the operator practises percussion preferably with the plex-

imeter and hammer. It is astonishing with how much greater clearness and intensity the sounds may be appreciated, and how much more accurately the outlines of the heart may be defined. I use this method more especially in trying to determine the diminution in the volume of the heart itself under the treatment by exercise. Of course, the stethoscope used in this way really acts as an ear-trumpet, but it is much more convenient than any ordinary ear-trumpet, because it leaves both hands free, and in no way interferes with the examination. I would not dwell upon a point which involves a principle so trivial if I had not satisfied myself by repeated observation of the real value of this method.

As to the cause of pericarditis, I have come to give a more important place to tuberculosis than is usually assigned to it. In my own experience most of my cases have occurred in subjects who came of tuberculous stock, who were members of tuberculous families, or who themselves subsequently showed signs of tuberculosis. I believe we shall have the same results with inoculation experiments, in dealing with the clear fluid, as were observed by Eichhorst and Aschoff in the case of the pleural effusions—that is, if we take the precaution which they did of injecting enough fluid.

The diagnosis is now become so much simplified by aspiration as to have multiplied the number of cases and led to a more proper appreciation of the frequency of the disease. We may remember, in making this observation, the complementary spaces determined by Rotch with melted butter, and subsequently confirmed by Ebstein—one at the second intercostal space and the other at the fifth intercostal space, to the right of the sternum. At these spaces any increase of fluid first shows itself. I make it a rule, in tapping, to insert the needle of the aspirator where I had got fluid with the subcutaneous syringe. I do not have any fear of hurting the heart. I have the impression now that I have always touched the heart at some time or other during the operation; if not at first, then as the sac empties itself and the heart floats up to the surface. But one becomes immediately conscious of touching the heart, and withdraws the instrument sufficiently to protect it. The danger of injury to the heart by this means has been much exaggerated, and the fear of the operation comes from the time when it was thought that the heart was an organ so important that it could not be diseased at all without taking life; in fact, Billroth, bold surgeon as he was, spoke of the operation of tapping the pericardium as a surgical frivolity and as a prostitution of surgical skill. A considerable experience has taught me to look more lightly upon this procedure; in fact, I have not much more hesitation in tapping the pericardium than in tapping the pleura, using always, of course, a syringe sterilized by absolute alcohol, which procedure tests the instrument also as to its working capacity.

DR. H. A. HARE: The danger of injuring the heart-muscle in tapping the pericardium is really not so great as many people think. I was confirmed in this belief by an unfortunate experiment involuntarily made by myself.

Some years ago I was very much interested in reading in the papers of an Italian's observation that men with wounds of the heart lived thirty-six hours after the receipt of the injury. To test the truth of this observation I undertook some experiments with dogs. I stabbed them in several places in the region of the heart, and I found that unless I struck a vital centre or punctured an auricle fatal results were never produced. If an ordinary knife be inserted into the ventricular wall and immediately withdrawn, the wound immediately closes. At the autopsies made on the dogs I found reparative changes going on. Unless we wound the heart very seriously and produce a hemorrhage, thus filling the pericardium with blood, or unless we strike a vital centre, there is less danger of injuring the heart than we are wont to think.

I had a case of a young man, eighteen or nineteen years of age, who was suffering from articular rheumatism. He had intense dyspnœa, with difficulty of heart-action. I asked Dr. Wilson to see him with me in consultation, and we decided that it was a case of pericarditis; and we concluded to tap the pericardium. I do not now remember the exact interspace at which we tapped him; perhaps Dr. Wilson may remember. We tapped him twice, and each time the boy seemed wonderfully improved. He died some days later. No autopsy was held, but I am convinced from the subsequent history of the case that it was not one of pericarditis, but of an enormously hypertrophied and dilated heart.

I would like to know whether it is the opinion of the members of this Association that digitalis should be given for pericardial effusion. It does not seem to me that it should. The drug increases the diastole, which is not desirable in this condition.

Dr. James C. Wilson said that the pericardium had been tapped in the fifth intercostal space on the left of the sternum.

Dr. T. M. Rotch: Although some of the gentlemen who have spoken seem to imply that wounding the heart, when tapping a pericardial effusion, is of little moment, yet I have known of a case where pricking the heart with an aspirator needle has caused sudden death. We should, therefore, guard against such danger in every way that is possible. It is well known that in certain cases the differential diagnosis between a dilated heart and a pericardial effusion is almost impossible by the usual methods of examination; therefore, it is in this class of cases that it is important to make an exploratory puncture in a locality where we are fairly sure that if it is a case of dilated heart the heart will not be touched. From a somewhat extended set of experiments performed on the cadaver I have shown that the fifth right interspace, 3 or 4 cm. from the right parasternal line, is a point where the effusion, if present, can often be reached, and where the danger of touching the heart is reduced to a minimum. No doubt there are instances where tapping in this locality will prove unsuccessful, but instances of unsuccessful

tapping where an effusion was present have also occurred when the point chosen was to the left of the sternum. I merely hold that it is better to make an exploratory puncture first to the right, and then, if not successful, to puncture in the other and more common points for operating. We must remember that the older the individual the more likely are we to have adhesions which may prevent the lung from receding before the fluid; and that, therefore, the younger the individual the more likely we are to reach the fluid when tapping on the right of the sternum. As it is still held by some writers that the heart is floated up by a pericardial effusion, it may be well to state that, in some careful experiments which I have performed in regard to this point, it has been clearly proved that the heart is never floated up by an effusion, but that it always sinks in the pericardial sac, and is in about the same position as when no effusion is present, so that the presence of an effusion does not lessen the danger of touching the heart when aspiration is performed at a point where the heart normally lies. I have recently had a case reported to me where a moderate pericardial effusion was present, and where the aspiration was done successfully in the fifth right interspace, with a subsequent recovery of the patient. In my wards in the Children's Hospital I had under my care a child with pericardial effusion. I carefully mapped out the area of dulness, and marked the point in the fifth right interspace where tapping should be performed if the general symptoms of the patient indicated aspiration. I left the patient with the house officer, with instructions to tap at that point if occasion should arise. After I left the hospital the symptoms became urgent, and the house officer, instead of tapping at once, went in search of some one to aid him in the operation, and on returning, as he entered the ward, the child suddenly died. He then immediately tapped in the fifth right interspace and withdrew two or three ounces of fluid. In regard to the diagnosis of pericardial effusion, the result of my clinical observations on this point is that those cases where the differential diagnosis between a dilated heart and a pericardial effusion is doubtful, the dulness in the fifth right interspace, 2 or 3 cm. from the right parasternal line, is of considerable aid in making the diagnosis. I should also like to refer to another point in the diagnosis of pericarditis with effusion, and that is that dulness may at times be found in the back between the angle of the scapula and the spinal column on the left side. I made this observation about ten years ago and never published it, and I claim no credit for it now, for the same fact has since been discovered and published by an English observer—Ewart.

DR. NORMAN BRIDGE: I am surprised that Dr. Shattuck, in the large number of cases he has observed (and I am sure he has seen more cases than I have), did not notice dysphagia as a symptom in any of his patients. I have seen it two or three times myself. In one case which came to autopsy there was no effusion of fluid, but a plastic deposit, an eighth of an inch thick, that was easily peeled off. In this case the dysphagia was the chief

first symptom of which the patient complained, and he complained of it bitterly. In another case, which did not come to autopsy, there was no great amount of effusion, but the dysphagia was distinct, though not marked.

DR. JAMES TYSON: There are one or two points in the paper which interested me a great deal. The first is in the matter of the outline of the dulness in pericardial effusion. I think Dr. Shattuck is rather too literal in his requirements for the triangular shape of the cardiac dulness in pericardial effusions. It is to be remembered that in all of these medico-anatomical points more or less latitude is allowed, and I think if we examine the shape of the dulness in Dr. Shattuck's pictures we will find that the triangular shape is approached. It is true that double enlargement of the heart—that is, of the right and left sides combined—gives a similar shape of dulness. I also want to refer to the phonendoscope as an aid to the mapping out of dulness in these cases. I think it is for such purposes that the usefulness of the instrument is especially manifest.

Again, I do not want to let this opportunity pass without referring to the blister which Dr. Shattuck has discarded in the treatment of pericarditis. I do not think we should let go of the blister in the treatment of this affection, and I believe that if the blister is applied sufficiently early we may even avert the effusion.

Finally, as to tapping, I have always had a great horror of tapping the pericardium, and have never done the operation nor had it done, but I was so much impressed by Dr. Shattuck's paper that my courage grew, and I thought I would tap in the very next case, but after hearing the experience of Dr. Hare and Dr. Rotch I fear I have gone back to where I was before.

DR. A. MCPHEDRAN: Our experience as to the frequency of pericarditis agrees more closely with that of Dr. Osler than of Dr. Shattuck. I desire to draw attention to the fact that the symptoms present in pericarditis, such as præcordial distress, dyspnœa, disturbed cardiac action, etc., are in reality due to the associated myocarditis. The fact that in some of Dr. Shattuck's cases the tappings were dry, or nearly so, renders it quite possible that the symptoms were due to myocarditis, with dilatation. Cases occur with the areas of præcordial dulness quite as great as in the diagrams presented, in which autopsy shows the condition to be due to dilatation following myocarditis, there being only fibrinous exudate in the pericardium.

DR. F. H. WILLIAMS: Allow me to direct attention to the assistance which may now be obtained by an x-ray examination in making a differential diagnosis between pericardial effusion and enlarged heart. Not only are the outlines different in the two cases, but in pericardial effusion the characteristic pulsations of the heart are, in some cases, not seen.

DR. E. G. JANEWAY: There are several points in this paper which I would discuss were there time, but I will confine myself to the following: in regard

to the pyramidal shape of the area of dulness or flatness, I rely upon it to distinguish pericardial effusion from an enlarged heart, especially upon the presence of dulness above the area where the enlarged heart would be found —from the third rib upward, when dealing with effusions of some size. So, again, the loss of vocal and of whisper resonance over such an area is an additional valuable sign in conjunction with the dulness or flatness, as above described.

On one occasion, in order to establish the diagnosis between dilated heart and pericardial effusion, there being absolute necessity for interference in case the latter were present, I aspirated blood from the heart without harm. The patient died later of heart-failure from overdistention, and the wound made had healed. One case, not in my own practice, has come under my observation, where an aspirating needle tore the heart, causing death. A layer of indurated phthisical lung over the pericardium had caused a simulation of pericardial effusion.

Dr. F. C. Shattuck, in closing the discussion, said: I simply want to say one word to correct a misapprehension of Dr. McPhedran. There was only one case that I tapped in which no fluid was obtained. There were dry taps in some cases, but there were also productive taps in the same patients.

SOME PRODUCTS OF THE TUBERCULOSIS BACILLUS AND THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS WITH ANTITOXIC SERUM.

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So much has been written in regard to the poisons of the tuberculosis bacillus that a review on this occasion would demand too much time, and we desire to refer only briefly to the work which is of importance in connection with those substances which we will describe.

Tuberculin, as is well known, is the extract of the tuberculosis bacilli, including the media upon which they are grown. From specially prepared artificial cultures of the tuberculosis germ Kühne[1] and the writer[2] (*Bulletin No. 7, Bureau of Animal Industry*) have obtained a substance corresponding to a nucleo-albumin which appeared to be the fever-producing principle of the germ. However, many conditions in tuberculosis were not accounted for by this substance, and as Mafucci,[3] Prudden and Hodenpyl,[4] Vissman,[5] and others had succeeded in producing tubercular nodules without necrosis by the intravenous injection of dead bacilli, it seemed as though it should be possible to isolate either from cultures or from bodies of the germs themselves some substance which might be considered accountable for the coagulation-necrosis of tissue which takes place—a necrosis which it appears is necessary for the progress of the disease. This problem was undertaken with the co-operation of my assistant, Dr. Dorset, more than two years ago. After many fruitless attempts we succeeded in isolating from artificial liquid cultures a crystalline substance having a melting-point of 161° to

164° C., readily soluble in ether, alcohol, and water, which separated from these solutions in needle-like or prismatic crystals (Plate I.) showing a slight yellow tint. They did not give the biuret reaction. The solution of this substance has an acid reaction to litmus, is acid in taste, and is optically inactive. The crystals give no precipitate with silver nitrate ($Ag.NO_3$), platinum chloride ($PtCl_4$), or barium hydrate ($Ba(OH)_2$). The analysis showed C = 50.88 per cent.; H = 6.70 per cent.; O = 42.42 per cent., giving a formula corresponding closely to $C_7H_{10}O_4$. This is the formula of teraconic acid, an unsaturated acid of the fatty series.

The culture-media upon which the germs were grown and from which these crystals were obtained contained potassium acid phosphate, ammonium phosphate, asparagin, and glycerine—the media used and described by one of us (de Schweinitz[6]) some years ago for studying bacterial products. After the germ has been growing on this media for some weeks the liquid becomes light yellow in color, having the appearance of a pale urine—a change which does not take place in the uninoculated media kept under the same conditions. Efforts to obtain this same acid from the ordinary beef-broth cultures containing peptone and glycerine resulted in securing minute amounts of the crystals only, which it was never possible to purify. After noting some of the other properties of this acid substance we came to the conclusion that the presence of peptone and the nitrogenous bases of the meat resulted in their combination with the crystals, forming compounds from which the acid could not again be easily extracted, even after the addition of acid. Finally, a small quantity of the crystalline substance obtained from the artificial cultures was added to the glycerine peptonized beef-broth media, but it was impossible to recover it again by the methods used for the first extraction, viz., repeated precipitation with alcohol and extraction with water and ether. The ready solubility of this substance in water as well as ether probably accounts for the difficulty of obtaining it. The uninoculated media did not yield these crystals. When dissolved in water and injected into guinea-pigs the following effects were noted. The injections were made subcutaneously in the thigh:

I. Healthy guinea-pigs: No. 314 received 0.015 gramme of crystals.
Temperature at time of injection 102.6° F.
Temperature, 11.50, one hour after injection, 100.6° F.

PLATE I.

Temperature, 1.30 P.M., 100.2° F.
Temperature, 3.00 P.M., 102.4° F.
Temperature, 4.00 P.M., 102.2° F.

During the above period breathing was rapid, with an occasional rigor.

Guinea pig No. 422. Weight 284 grammes; received 0.0095 gramme of crystals at 12.05 P.M.

Temperature at time of injection 99.8° F.
Temperature at 2.30 P.M. 97.4° F.

On the next day there was quite perceptible swelling where the injection was made. Pig was chloroformed at end of twenty-four hours and showed considerable inflammation at seat of injection. Tissues were hemorrhagic and bathed in a serous exudate. The muscular tissue was much disintegrated, resembling the appearance from the action of a caustic.

Guinea-pig No. 511. Weight 183 grammes; received 0.0048 gramme in ½ c.c. water at 11.25 A.M., subcutaneously in thigh.

Temperature at time of injection 103° F.
Temperature at 12.25 P.M., one hour after, 101.8° F.
Temperature at 1.15 P.M. 102° F.
Temperature at 3.25 P.M. 100.8° F.

Chloroformed next day. Considerable inflammation, with serous exudate at seat of injection.

Guinea-pig No. 10 received 0.0274 gramme at 10.10 A.M.

Temperature at time of injection 99.2° F.
Temperature at 10.40 A.M. 100.2° F.
Temperature at 11.15 A.M. 100.6° F.
Temperature at 11.50 A.M. 100.6° F.
Temperature at 2.00 P.M. 100.2° F.

During above period this pig showed signs of restlessness, breathed rapidly and shivered.

II. Tuberculous guinea-pigs:

Guinea-pig No. 181 received 0.017 gramme at 10.25 A.M.

Temperature at 11.40 A.M. 101.4° F.
Temperature at 1.50 P.M. 102.8° F.
Temperature at 2.50 P.M. 103.4° F.
Temperature at 3.50 P.M. 103° F.

Pig sat drawn up in cage, and shivered.

Guinea-pig No. 259 had received virulent tuberculosis two weeks previous to injection of crystals. Received 0.0172 gramme at 10.45 A.M.

Temperature at time of injection 102.4° F.
Temperature at 11.45 A.M. 101.6° F.
Temperature at 3.20 P.M. 101.6° F.

Distinct rigors and rapid breathing.

Guinea-pig No. 377 inoculated with sputum from tuberculous patient some time before injection of crystals. Received 0.023 gramme at 11.35 A.M.

Temperature at time of injection 101.2° F.
Temperature at 11.35 100.6°

Trembling very noticeable.

Guinea-pig No. 11 had been inoculated with attenuated and virulent tuberculosis culture (weight 448 grammes). Received 0.0096 gramme of crystals at 11.25 A.M.

Temperature at time of injection 103° F.
Temperature at 12.25 P.M. 100.8° F.
Temperature at 1.15 P.M. 101° F.
Temperature at 3.25 P.M. 100.8° F.

The idea was suggested from these experiments that this acid, evidently a secretory product of the bacillus, was one of its most powerful weapons; that by its action upon the tissue the cells were first destroyed, so that they could subsequently be utilized by the germ as food, and in this way the germ protected itself from surrounding leucocytes. To test this, crystals dissolved in sterile water were injected by means of a hypodermic syringe directly into the liver. At the same time an equal quantity of water was injected into a check in the same way. After forty-eight hours check and experimental animals were killed. The check failed to show any effect, while the others exhibited a liver with several light spots. A repetition of this experiment gave the same results.

No effort was made to recover these cyrstals from the liver, as the amount used was too small. We did not test the effect upon the liver by an intravenous injection, as would otherwise have been done, because we had found that there was a combination of this acid substance with the albuminoids or bases, and any intravenous injection would have resulted in its immediate conversion into a modification by uniting with the albuminoids in the blood. Further, the growth of the germ in the body is localized, and where localized the necrotic areas are apparent, so that the fairest test was to bring the substance as soon as possible in contact with the tissue. The experiments in injections of the animals and appearance of sections follow.

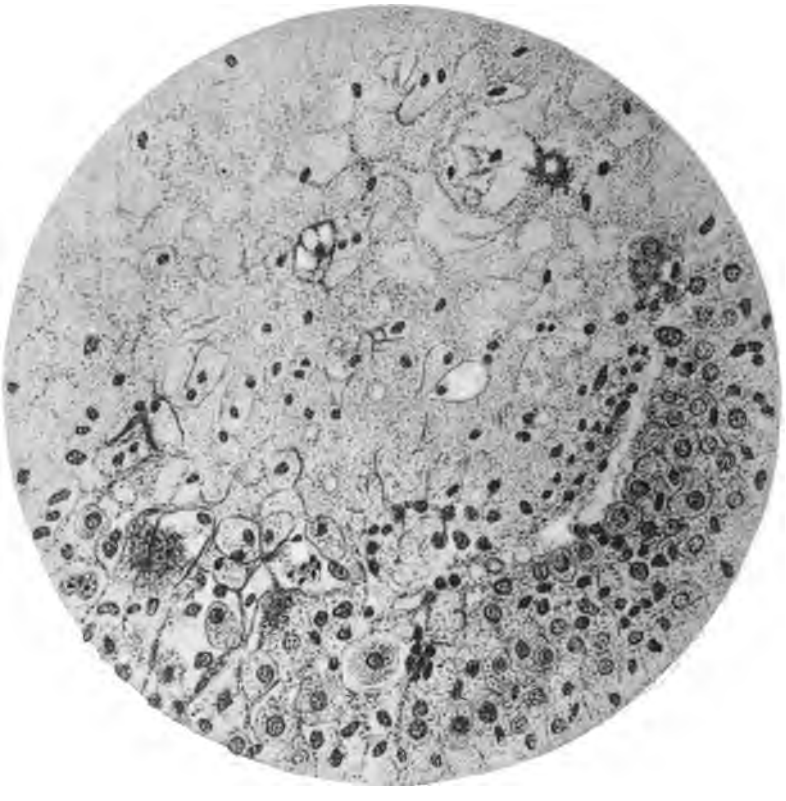
Injection of crystals from artificial cultures of B. tuberculosis into the liver of guinea-pigs:

Guinea-pig No. 409 received 0.00178 gramme in liver on left side at 11.45 A.M. Pig weighed 338 grammes.

Temperature at time of injection 101.6° F.
Temperature at 3.00 P.M. 102° F.

Chloroformed October 24, 1896, at 12 M. Liver dark, with one or two small

PLATE II.



white spots in it, and apparently a small inflamed spot at about the position where injection was made. Gall-bladder injected and seemingly inflamed.

Guinea-pig No. 412 received 0.0037 gramme in liver at 1.45 P.M. Pig weighed 242 grammes.

Temperature at 1.45 P.M. 103° F.

Temperature at 3.30 P.M. 100.4° F.

Chloroformed at end of forty-eight hours. Gall-bladder was congested (not so much as in No. 409). Liver showed pale spots and one or two small white areas of apparent necrosis. Hardened in $HgCl_2$ on microscopic examination one area rather well defined where the liver-cells do not take hæmatoxylon well, though nuclei stain, could be seen.

Checks on injection of crystals into liver.

Guinea-pig No. 510 received ½ c.c. sterile distilled water in liver.

Chloroformed after forty-eight hours. Post-mortem, all organs, liver, lungs, spleen, etc., normal.

Guinea-pig No. 387 received ½ c.c. sterile distilled water in liver. Chloroformed after forty-eight hours. Post-mortem. All organs normal excepting one or two very small pale spots in liver; no necrosis.

Injection of crystals. Guinea-pig "C" received 0.0043 gramme in liver. Chloroformed after six days. Pig weighed 600 grammes.

Lungs very slightly congested. In large left lobe of liver there were two or three comparatively large areas of necrosis. These spots were on the side in which injection was made, and the liver appeared to show the track of needle. The guinea-pig was otherwise healthy.

Guinea-pig "E" received 0.0023 gramme of crystals in liver. Chloroformed after two days. Pig weighed 345 grammes.

All organs appeared normal, except stomach, which showed a slight inflammation in its wall on the side which lay next to a necrosed spot in the liver.

Besides this spot there were several others of considerable size in the liver on the side on which the injection was made. The section of pig "C," the one allowed to live six days after injection, showed on microscopic examination the following:

Stained with hæmatoxylon and eosin; distinct areas of necrosis were noted, the most marked ones near the surface of the liver. Polynuclear leucocytes were present, though not in large numbers, in and around the necrotic areas, and there was also an increase in connective-tissue cells of the liver around these same areas. Plate II. is a drawing of the liver section, showing healthy and necrosed areas.

Prudden,[7] 1892, suggests that caseation, so constantly present in tuberculosis, is probably due to a specific metabolic product of the bacillus.

It seems very reasonable to conclude from our experiments that we have here the substance formed by the bacillus which is responsible for this necrosis.

The formula which can be deduced from the analysis makes this acid correspond closely to teraconic, which has some properties very similar to those noted by us in connection with this new acid. Its identity we have not yet proved or disproved, as the preparation of teraconic acid is not completed. The amount of this acid obtained is very small, so that we have used only a very minute amount of it for testing its immunizing property. A single injection of 0.0020 gramme was sufficient to keep the animals alive some weeks longer than the checks, and its solution appeared to exert some slight bactericidal influence.

As this substance seemed to be a temperature-reducing principle in healthy and diseased animals, we endeavored to separate the fever-producing principle independently. The crystals were always found in the culture-liquid, and only minute amounts could be obtained from the germs themselves that had been grown on liquid media. Accordingly these bacilli, carefully filtered, without heat, were washed in cold water and next extracted with hot water. This hot-water extract contained an albuminoid which caused the tuberculin reaction in tuberculous guinea-pigs and calves upon repeated injections.

Roux and Nocard[8] claim that they have a tuberculin which will give reactions almost indefinitely, but do not describe its method of preparation. Whether this is the same substance that we have obtained we are unable to say, but certain it is that the tuberculin prepared in the way we have indicated will give reactions four to five times and more in succession, where the reaction with tuberculin as prepared in the ordinary way fails after the second time. The conclusion is a fair one. We think that the fever-reducing principle having been removed to an extent, if not entirely, the immunity to the fever-producing principle is much more slowly acquired. Our tests upon guinea-pigs and tuberculous calves were made with only one day intervening between the injections. See Table I.

In the *Deutsche med. Wochenschrift*, April 1, 1897, Dr. R. Koch[9] describes some new tuberculin preparations. The dried tuberculosis bacilli were taken (the culture media used is not mentioned), finely powdered and centrifugalized with distilled water. The opalescent solution obtained tested upon animals gave the tuberculin reaction.

The residual germs were submitted to this treatment a number of times until finally all were practically dissolved. The latter solutions in large doses caused a reaction, but in small quantities did not produce this result, and seemed to exert both an immunizing and curative action in experimental tuberculosis. Koch used for this work virulent germs, and claims that attenuated germs do not give an active product. Our own work was done with germs purposely attenuated by cultivation, and the results show that a very active fever-producing, fever-reducing, and probably curative principle can be obtained from them. It hardly seemed justifiable to ourselves or others to powder dried virulent germs and have the dust floating in the air. Koch further refers to two fatty acids, which, in conjunction with Proskauer,[9] had been found in the bodies of the germs. The writers[10] of this paper published in August, 1895, a preliminary study of the fats of the tuberculosis bacilli, showing the high content of fat in the body of these germs, which accounts for the difficulty in staining them with certain colors, as well as their difficult absorption.

In a later paper,[11] 1896, we described briefly the different acids obtained from the body of the germ—both high melting and low melting acids—but whether or not these are identical with those observed by Koch and Proskauer we cannot tell from the brief mention they have made of them.

From our results it seems very reasonable to think that the necrotic acid is the fever-reducing principle, the albuminoid the fever-producing principle, and the reason the ordinary tuberculin does not react continuously is on account of the presence of both of these substances at the same time. At any rate, tuberculous guinea-pigs tested successively with tuberculin showed no reaction, while with this albuminoid, which we will call cell-extract, a reaction was obtained.

The preliminary experiments published by one of us[12] in 1894 upon the production of an immunity or resistance to tuberculosis by attenuated cultures have been continued, and are confirmatory of the first results, showing the production of great resistance and in some cases complete immunity. A detail of two sets of these experiments may be given as an instance of their general results. (Table II.)

The first effect of the injection of the attenuated germ was in some instances to cause a slight decrease in weight, sometimes a local swelling was noted at the point of injection, and occasionally an enlargement of the inguinal glands. This disappeared after some weeks. This local swelling is probably due to the mechanical action of the bodies of the germs, on account of their high fat content and possible presence of a minute amount of the acid, causing necrosis. It does not always result from a subcutaneous inoculation, and an apparent immunity to this action is acquired by repeated injections. This is well shown in horses and cows submitted to treatment with the attenuated germ.

From six to eight weeks after the date of the injection of the germ guinea-pigs seem to be entirely well, and are then inoculated with the virulent germ. As can be seen from the chart, the checks died within six weeks from date of inoculation, while the others vaccinated remained well four months afterward. It has appeared from many experiments that if the inoculation with the virulent bacillus is made before complete recovery from the treatment with the attenuated bacillus the resistance is considerably less. The inoculation of the animals with the virulent bacillus, and subsequently with a single injection of the attenuated bacillus, showed that the latter produced a slight resistance, but no very material retardation of the disease.

The production of this partial immunity or artificial resistance by means of the attenuated cultures suggested already, in 1894, the availability of this same material for the purpose of treating animals for the production of a serum which would have some effect in curing tuberculosis. It suggested the idea further that possibly cattle could be vaccinated with this attenuated germ and made immune to tuberculosis.

Two cows and one heifer were selected for the work, which was conducted for us by Dr. Schroeder, in charge of the Experiment Station of the Bureau of Animal Industry. One of these animals was originally tuberculous, the other two healthy. The tuberculous animal received large doses of tuberculin until it had received altogether 19,407 c.c. (nineteen and one-half liters), and as much as 1500 c.c. of tuberculin at a single dose, from November, 1894, to April 20, 1897. The other animals received injections of the at-

tenuated culture, the amount injected in fifteen months being 11,425 c.c. and 18,100 c.c., respectively; and by this is meant the liquid culture-media *in toto*, including the germs, just as taken from the incubator, without any further treatment. At first the injections produced a slight reaction and occasionally a local œdema and abscess. After they had been continued for some time this effect diminished or disappeared. The serum of all of these animals was tested a number of times. Guinea-pigs were injected with the serum in quantities varying from 1½ to 6 c.c., and subsequently inoculated, together with the checks, with a culture sufficiently virulent to kill the checks within four or five weeks, or the pigs were inoculated with the virulent bacilli and treated by subsequent injections of the serum. Without giving the detail of the experiments, we may say that the serum from the cow treated with tuberculin would cause in the pigs a slight resistance to the disease; the serum of those treated with the attenuated bacilli produced more resistance on the part of the animals or prolonged their life to some extent, but not sufficiently, as compared with the quantity of material injected, to make the use of cow-serum appear practicable. The cow-serum, although sterile, frequently produced abscesses in guinea-pigs. This serum we expect to test again shortly, when it should be more potent.

While these experiments were in progress two horses had been pressed into service They were treated by injecting the attenuated cultures, culture fluid, and bacilli. The first injection of 5 c.c. caused a decided temperature-reaction, local œdema, stiffness, slight loss of appetite, recovery after a few days. At first local abscesses were formed, which healed fairly readily. After a time the abscess-formation ceased or occurred occasionally. After eight months' treatment, the doses of the culture being gradually increased up to 300 to 400 c.c.—the total amount injected in fifteen months = 4459 c.c.—the serum was used for testing. It separated out clear and well. Two sets of illustrations may be given to show its action on tuberculous animals. (Table III.) In one set the checks and two treated pigs died; the other two treated pigs are alive and in perfect health, apparently, after a number of months. In another set the checks—four in number—died within four to five weeks, while the treated ones lived two or three weeks longer, showing, on autopsy, much

less disease in the lungs than the checks. We endeavored further to isolate from the serum antitoxic substances by a slight modification of the Brieger-Boer method. We finally succeeded in obtaining a small quantity of a grayish powder, giving the biuret reaction, soluble in water with difficulty, which was used for treating guinea-pigs in the same way as the serum. The result was as in the first instance. The pigs—one-half pound in weight—were inoculated with a virulent germ and treated by a single injection of 0.008 gramme of this solid substance. They lived three to four weeks longer than the checks, again showing considerable less disease in the lungs and less necrosis in the liver.

The effect of the serum was also tried in preventing the rise of temperature in tuberculous guinea-pigs and in saving them from a fatal dose of tuberculin. As can be seen from the temperature-reactions in Table I., the injections of $\frac{1}{4}$ c.c. of diluted tuberculin and at the same time of $\frac{1}{2}$ c.c. of the serum, either caused a decided reduction of the temperature or prevented a characteristic tuberculin reaction in animals weighing about 400 grammes.

The result of all this work leads us to the conclusion that the injection of the liver culture in healthy animals produces substances antitoxic to tuberculosis; that the quantity of this substance can be increased gradually; that the treatment of tuberculosis is and will be for some time still in the experimental stage. One point, however, must be remembered, viz., that while it may be difficult to cure the disease in a guinea-pig, where its course is very rapid, virulent bacilli requiring only from four to five weeks to kill, it might be much easier to check the disease when more prolonged in action, as in the majority of cases in man. Again, in addition to some form of specific treatment for the disease, man usually has the advantage of being placed under the best possible surroundings as to diet, climate, etc., and every effort is made to aid the improvement of the patient, while with experimental animals the conditions are different. The experimental results obtained lead undoubtedly to the conclusion that while the treatment with antitoxic serum is still in the experimental stage, and should as yet be used only in sanitariums and under the best conditions, we are on the road to success in the treatment of this disease and nearer our goal than ever before.

In an experimental way, the antitoxic serum as prepared in my laboratory has been used by Dr. Stubbert at the Loomis Sanitarium, and some by Dr. Trudeau at Saranac Lake, as well as by Dr. Charles W. Richardson in this city.

The serum used for these cases was of the same lot that cured the guinea-pigs reported in Table III. The treatment has not been continued long enough for positive conclusions to be drawn. One of the cases reported by Dr. Stubbert has been apparently cured and the others much improved. Dr. Charles W. Richardson, of this city, reports decided improvement in the cases upon which this serum has been used. Dr. Trudeau has not used the material long enough to come to any definite conclusions. He noted reduction of high temperatures under its influence in several of the cases tried.

Maragliano, Babes, and Behring are the other principal workers in the preparation of an antitoxic serum for tuberculosis. Paquin also has an antitoxic serum on the market.

Maragliano[13] (*Revue de la Tuberculose*, Juillet, 1896, p. 131) gives the method he has used for the production of antitoxic serum, and notes that there is present in the cold filtered cultures of the tuberculosis bacilli a substance which causes the reduction of temperature, and another, not destroyed by heat, which causes the rise of temperature. In all probability, without isolating the principle, Maragliano was using solutions of the crystalline substance we have described in the beginning of this paper. While this is not destroyed by heat, as he seems to think, it does undergo some change by combining probably with the albuminoid matter in the media, and thus losing its distinct property as a temperature-reducing substance; or, more probably, its temperature-reducing property is disguised by the presence of the temperature-producing principle extracted by hot water. The serum which he obtains from treatment of the animals with the different products of the bacilli is claimed to have some effect in reducing the temperature and apparently improving the disease.

In the *Zeitschrift für Hygiene*, Babes,[14] reviewing a portion of the work upon the treatment of tuberculosis with serum, comes to the conclusion that he is the first individual to have discovered any antitoxic properties in this serum; that there is an antitoxic substance

present in treated animals, but that it has not yet been brought to a sufficient development to warrant general use.

Our experiments lead us to conclude that while the injection with tuberculin in healthy animals produces a serum containing antitoxic material, the amount of this is small, and that the injection of the live culture is the proper treatment. We cannot agree with the statement made that horses are unsuitable for the work. Mules and donkeys may perhaps give quicker results, but horses seem to be eminently satisfactory. At no time have we found that the horse-serum produces toxic effects, although this has been noted in the cow-serum.

If the antitoxic serum-treatment for tuberculosis could be freed for the present from its commercial aspect, and careful, systematic experiments continuously conducted in numerous hospitals and sanitariums, this or a similar modified method of treatment could be looked to for good results. When tuberculosis can be uniformly cured in guinea-pigs as certainly as diphtheria, then does the commercial aspect become a fair and legitimate one.

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TABLE I.—TEST OF CELL EXTRACT, TUBERCULIN, AND SERUM.

Date.	No. of Animal.	Condition.	Weight in grams.	Substance injected.	Temperature.		
					A.M. 11.20	P.M. 1.40	P.M. 3.05
March 26	XI.	Tuberculous Guinea-pig.	423	¼ cc. tuberculin + ⅓ cc. serum.	103.2°	96.6°	96.2°
	492	Tuberculous Guinea-pig.	255	¼ cc. tuberculin.	102.8	105.0	104.4
	VIII.	Attenuated, tuberculous.	443	¼ cc. tuberculin + ½ cc. serum.	101.0	102.4	103.8
	XIX.	Attenuated, tuberculous.	356	2 cc. cell extract = 0.0040 gram.	102.2	105.6	103.4
	513	Healthy (check)	210	1 cc. cell extract = 0 0020 gram.	101.4	101.6	101.0
					A.M. 10.50	P.M. 12.25	P.M. 1.50
March 27	XI.	Tuberculous Guinea-pig.	...	¼ cc. tuberculin.	101.2°	102.4°	102.4°
	492	Tuberculous Guinea-pig.	...	2 cc. cell extract = ¼ cc. tuberc.	103.0	103.8	105.0
	VIII.	Attenuated, tuberculous.	...	¼ cc. tuberculin.	103.0	103.2	103.8
	XIX.	Attenuated, tuberculous.	...	¼ cc. tuberculin.	102.8	103.8	103.0
	XX.	Attenuated, tuberculous.	...	¼ cc. tuberculin + ½ cc. serum.	102.4	95.0	95.0
					A.M. 10.25	P.M. 12.10	P.M. 1.45
March 29	VIII.	Attenuated, tuberculous.	...	2 cc. cell extract = ¼ cc. tuberc.	101.8°	103.8°	103.6°
	492	Tuberculous Guinea-pig.	...	2 cc. cell extract = ¼ cc. tuberc.	102.8	104.4	104.6
	XIX.	Attenuated, tuberculous.	...	2 cc. cell extract = ¼ cc. tuberc.	102.2	105.6	103.0
					A.M. 10.45	P.M. 12.15	2.10 P.M.
March 30	492	Tuberculous Guinea-pig.	...	2 cc cell extract = ¼ cc. tuberc.	102.2°	104.2°	104.2°
	XIX.	Attenuated, tuberculous.	...	¼ cc. tuberculin.	102.2	103.2	103.6

TABLE II.—TWO SETS OF EXPERIMENTS SHOWING THE AVERAGE RESULTS IN EXPERIMENTS IN WHICH THE GUINEA-PIGS WERE VACCINATED WITH ATTENUATED BACILLI AND THEN INOCULATED WITH VIRULENT BACILLI.

No.	October 24. Inoculation and amount of attenuated germ.	Weight. Oct. 24	Weight. Nov. 2	Condition.	December 9. Inoculation and amount of virulent germ.	Weight. Dec. 16	Weight. Jan. 7	Weight. Jan. 19	Weight. Feb. 2	Weight. Feb. 8	Weight. Apr. 8	Weight. Apr. 19
373	1½ cc. 50th generation	12 oz.	14 oz.	O. K.	Dead from pneumonia							
374	" " "	10 "	11 "	"	⅛ cc. of vir. tuberculosis 4th generation from rabbit.	14 oz.	16 oz.	16 oz.	15¼oz.	16 oz.	16 oz.	14 oz.
375	" " "	16 "	15 "	"	Dead from pneumonia							
376	" " "	16 "	14½"	"	⅛ cc. of vir. tuberculosis 4th generation from rabbit.	12 "	15 "	15 "	15 "	15 "	17½"	18 "
377	Check	13 "	13¼"	"	" " "	12 "	13 "	12½"	Dead			
378	1½ cc. attenuated germ	14 "	14 "	Thin	Dead from pneumonia							

No.	Dec. 21	Dec. 26	Dec. 21	Feb. 2	Feb. 12	Mar. 6	March 8	Mar. 16	Apr. 6	Apr. 19	Apr. 21
II.	½ cc. of 61st generation	1½ cc. of 61st generation	13 oz.	14 oz.	16 oz.	.....	⅛ cc. virulent germ.	16 oz.	Chloroformed		
III.	" "	" "	12 "	15½"	14 "	.....	" " "	17 "	17 oz.	19 oz.	
IV.	" "	" "	15 "	16 "	17 "	.....	" " "	20 "	21 "	20 "	
V.	" "	" "	13 "	15 "	16 "	.....	" " "	17½"	19 "	19 "	
VII.	" "	" "	14 "	13 "	14 "	.....	" " "	16 "	16½"	18 "	
VIII.	" "	" "	15 "	15 "	16 "	.....	" " "	17 "	16 "	18 "	
IX.	" "	" "	12 "	13 "	11 "	.....	" " "	14 "	15 "	16 "	
X.	(Check)	(Check)	.....	16 "	16 "	18 oz.	" " "	17½"	14 "	12 "	Dead
XI.	(Check)	(Check)	.....	15 "	16 "	17 "	" " "	17½"	Dead		
XII.	½ cc. of 61st generation	1½ cc. of 61st generation	16 oz.	16 "	16 "	.....	" " "	18 "	19 oz.	19 "	
XIII.	" "	" "	14 "	15 "	16 "	.....	" " "	18 "	17½"	16½"	
XV.	" "	" "	15 "	16 "	18 "	.....	" " "	18 "	14 "		
XVI.	" "	" "	15 "	15 "	17 "	.....	" " "	18 "	18½"	20 "	
XVII.	" "	" "	12 "	12 "	13 "	.....	" " "	15 "	15 "	14½"	
XVIII.	" "	" "	15 "	15 "	14 "	.....	" " "	16 "	17½"	17½"	
XIX.	" "	" "	14 "	13 "	18 "	.....	" " "	13 "	13 "	12½"	
XX.	" "	" "	15 "	18 "	14 "	.....	" " "	20 "	19 "	19 "	

TABLE III.—EFFECT OF SERUM FROM HORSE INJECTED WITH ATTENUATED CULTURE ON TUBERCULOUS GUINEA-PIGS.

No.	Weight.	October 24. Amount of virulent culture and serum injected.	Dates and amount of serum injected.				
			November 16	November 17	November 25	Dec. 8	Dec. 8	April 19
434 (check)	10 oz.	¼ cc. of vir. tuberc. cult.	10 oz.	8½ oz.	8 oz.	Dead		
435	9 "	" " " " 1½ cc. of serum.	9 oz. + 1½ cc.	8 oz. + 1½ cc.	8 oz. + 1½ cc.	.....	9 oz.	20 oz.
436	11 "	" " " " " " "	10 " " "	9 " " "	7 " " "	Dead		
437	14 "	" " " " " " "	13 " " "	11 " " "	10 " " "	.....	10 oz.	20 oz.
438	9 "	" " " " " " "	8 " " "	8 " " "	6 " " "	Dead		
439	8 "	" " " " " " "	8 " " "	7 " " "	5 " " "			

TABLE IV.—TEST OF DRY ANTITOXIC MATERIAL FROM SERUM FROM VACCINATED HORSE.

No. of animal.	Weight.	Date.	Material for inoculation.	Date.	Weight.	March 8.	Date.	Weight.	Date.
464	Check 11 oz.	Feb. 4	⅛ cc. tuberc. virulent	Feb. 20	11 oz.	.....	Mar. 6	10 oz.	March 8. Dead.
476	12 "	" 4	⅛ cc. tuberc. virulent + 0.208 gr. antitoxin	" 20	12 "	.....	"	10 "	" 16. Dead; less disease than others.
478	Check 8½ "	" 4	⅛ cc. tuberc. virulent	" 20	8 "	Dead; tuberculosis.			
479	" 8 "	" 20	⅛ cc. tuberc. virulent	.....	.....	.....	"	7 "	" 8. Dead; generalized tuberculosis.
481	" 10 "	" 20	⅛ cc. tuberc. virulent	.....	.....	.....	"	9 "	" 12. Dead.
482	13 "	" 20	⅛ cc. tuberc. virulent + 0.008 gr. antitoxin	.....	.....	.....	"	12 "	April 7. Dead; less disease than others.
484	12 "	" 20	⅛ cc. tuberc. virulent + 0 008 gr. antitoxin	.....	.....	.....	"	12 "	" 12. Dead; less disease than others.

ON THE OCCURRENCE OF PRIMARY TUBERCULOSIS OF THE KIDNEY, WITH SPECIAL REFERENCE TO A PRIMARY MILIARY FORM.

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At the inception of a study of the subject of tuberculosis of the kidney we appreciate the fact that under the same generic term are grouped certain diverse, morbid conditions having nothing in common but their mutual dependence upon the same morbific agent—the tubercle bacillus of Koch. The varying manifestations of tuberculosis of the kidney differ not only as to the time of their occurrence with respect to other possible tuberculous lesions in the body, but also as to their pathological anatomy, their symptomatology, their diagnosis, their prognosis, and their therapeutic indications. The implication of the kidney in the tuberculous process has interested numerous investigators for a very long time, but their observations were usually limited to those cases in which the renal involvement was secondary to some other well-established tuberculous lesion in the body. It is but recently—within the past half-century—that the possibility and the fact of the occurrence of primary renal tuberculosis have received more than cursory attention; and it is the outcome of these recent studies that has resulted in the establishment of the fact that many cases of renal tuberculosis of supposedly secondary involvement are in reality instances of primary infection. Because of this fact, and reasoning from analogy, one is led to the not unwarranted supposition that primary renal tuberculosis is much more common than is usually assumed.

As is well known, tuberculosis of the kidney manifests itself in either of two general and quite distinct forms—either as miliary tuberculosis or as caseous tuberculosis—the latter a condition variously described as chronic tuberculosis, chronic localized tuberculosis, renal or nephro-phthisis, tuberculous pyelitis, tuberculous pyelo-nephritis—the strumous or scrofulous kidney of the older writers. It is now generally admitted that the latter—that is, caseous tuberculosis of the kidney—may be a primary or a secondary affection; whereas the former—miliary tuberculosis—is commonly regarded as being always the result of secondary infection.

Miliary tuberculosis of the kidney is an acute process, and is generally believed to affect both kidneys. It occurs sequentially to tuberculosis of any of the bodily organs, especially of the lungs, glands, or meninges; less commonly the bones, joints, bladder, prostate, etc. It occurs in association with the general dissemination of miliary tubercles throughout the system—in the liver, spleen, lungs, serous membranes, etc. Infection usually takes place by means of the bloodvessels, though if the primary focus be in the lower urinary tract it is not impossible that infection may take place *via* the lymphatics, under which circumstances a unilateral involvement might ensue. The implication of both kidneys is, however, the rule, and there exists a tendency to the simultaneous involvement of more or less of the entire genito-urinary tract. The condition is quite common in the young, and is characterized by the development of varying numbers of small, whitish semi-translucent spots, which later develop into grayish-white or yellowish tubercles, which are generally surrounded by a zone of deeply congested renal tissue. As the infection in these instances is hæmatogenic, the tubercles are usually found most numerously in the cortex, where the bacilli become arrested in the terminals of the renal artery. But they vary much in number, and are not uncommonly distributed without any evidence of regularity. Sometimes they are arranged, as it were, in rows, in the direction of the vasa interlobularia, and other instances have been recorded in which they seem to be confined to the region supplied by one branch of the renal artery. They usually remain isolated, evincing but little tendency to run together, nor do they show the marked tendency to degenerate so characteristic of the caseous form. Rarely larger areas are formed by the

coalescence of several smaller ones. Through tubercular implication of the walls of the arteries thrombi sometimes are formed, giving rise to anæmic or hemorrhagic infarcts; and at times the arrangement of the miliary tubercles in rows in association with the fatty degeneration of the neighboring renal parenchyma presents also an appearance not unlike infarcts, but the discovery of the small tubercles prevents the error. Microscopically, the tubercles are frequently noted in the Malpighian corpuscles, in which and in the adjoining uriniferous tubules the tubercle bacilli may be detected. The tubercles consist at first of small, roundish areas of epithelioidal cells and round-cell infiltration, in the beginning, at least, quite well circumscribed. Later, giant-cells make their appearance, the epithelium of the uriniferous tubules participates in the process, undergoing fatty degeneration, and finally breaking down into a fatty detritus, upon which the entire area may exhibit degenerative changes more or less marked.

As this variety of tuberculosis of the kidney gives rise to few or no manifest disturbances with the function of the kidney or of the urinary bladder, and as it is part of a general process of miliary tuberculosis which of itself gives rise to much more obtrusive symptoms than could the kidney lesion, the kidney involvement possesses but little clinical interest or importance. It can hardly be diagnosticated, although Rosenstein is said to have observed anuria in children under such circumstances. The condition is, however, usually not suspected prior to the post-mortem. Further, were it possible of detection there would be no utility therein, as it is not amenable to any kind of treatment.

In contradistinction to this the usual form of miliary tuberculosis of the kidney—a secondary affair—there is another class of cases in which miliary tuberculosis of the kidney occurs as a primary affection and involves but one kidney. This class of cases must be of some rarity, as they are usually not referred to. Knowsley Thornton and Newmann make mention of the possibility of their occurrence, and Rosenstein and others suggest that the ordinary caseous variety may in its beginning present itself in the miliary form. But primary unilateral miliary tuberculosis of the kidney has nevertheless received scant notice. The usual implication of the kidney in the tuberculous process presupposes a tuberculous implantation

in a kidney previously healthy. True, some few instances of mixed infection have been hinted at, and other cases of calculous pyelitis, for example, associated with tubercular disease of the kidney, have been reported. But the occurrence of a primary circumscribed unilateral miliary tuberculosis of the kidney, and in a patient the subject of chronic nephritis, is considered sufficiently unique to justify the report of the following case observed in the private practice of one of us (Dr. Stewart):

J. H. K., a female, aged forty-five years, married, consulted Dr. Stewart October, 1894, for presumed cardiac trouble. One year previously she had suffered a mild attack of articular rheumatism, which is said by her attending physician to have affected her heart. This, it had been presumed, accounted for the extreme and distressing breathlessness and palpitation of which she complained. It was stated that her health had always been fair until lately. The attack of rheumatism was said to have been slight. She had suffered considerably from headache during the past year and lately from attacks of severe dyspnœa. These latter were becoming more frequent and pronounced, and amounted at times to the most distressing orthopnœa. Dyspnœa did not seem to be induced by exertion, and was most common during the night. Cough was absent save at the time of some of these attacks.

The patient was of spare build, of medium height, of brunette type, of nervous temperament, and weighed 115 pounds. Anæmia was apparently so slight that a blood-examination was omitted. Physical examination of the heart showed the impulse to be extended. There was audible a murmur, somewhat harsh, whistling in character, and systolic in time. Although readily discernible at the apex, its seat of greatest intensity was in the tricuspid area. Transmission to the left, other than to a very limited extent, did not occur. The murmur was inaudible beyond the apex. There was marked accentuation of the second sound at the apex. At the base it was more distinct at the right than at the left. Very high blood-pressure was apparent and persisted even after resort to very active purgation and the free use of arterial sedatives. The arteries were tense and of fair volume. The radial pulsation was not readily extinguished by pressure. The accompanying sphygmogram shows the condition of raised arterial tension usual:

The lungs gave no indication of primary disease. Signs of passive congestion, posteriorly, chiefly at the right base, were common.

The abdominal viscera presented no indications of abnormalities.

An examination of the urine, made a few days after the patient was seen for the first time, showed a rather heavy sediment, which was found to consist chiefly of pus. There were present also a few epithelial casts, a number of fine and coarse granular casts, and hyaline cylinders and cylindroids.

The presence in the urine of pus in some amount, which repeated examinations showed to be usual despite any obvious bladder or vaginal condition to occasion it, naturally suggested the thought of tuberculosis of the urinary passages complicating a very obvious chronic nephritis. The patient was totally free from leucorrhœa. It is of interest also to relate that although she had been married some twenty years, and was living happily with her husband, who was devoted to her, she was still a *virgo intacta*. The hymen was later found to be perfectly preserved; sexual connection, it was related, had never occurred.

The first search made for tubercle bacilli disclosed them in large number, presenting themselves commonly in typical clumps. These were subsequently repeatedly found both by Dr. Stewart and by his assistant in laboratory work, Dr. Pottberg. Differentiation from smegma bacillus was of course carefully made. When the case first came under observation the urine was apt to be turbid when voided, of low acidity, and readily decomposable. Subsequently perfectly clear specimens were passed, depositing pus as formerly. A number of examinations of the mixed urine showed that albumin was present, commonly in about $\frac{1}{10}$ per cent. by weight. An account of the daily twenty-four-hour output was taken for two or three days weekly during the greater part of the time the case was under observation, both to maintain a watch on nitrogenous excretion and to determine as to a possible pyo-nephrosis. There were at no time indications of blocking of the ureter. The amount voided was commonly between 750 and 900 c.c. It was readily increased by diuretics. The specific gravity was usually moderately low, as was the urea output. The latter, for her weight, should have been 25 grammes; while even under full diet and diuretics it did not exceed 14 grammes, and was commonly less.

The case was early diagnosticated as one of chronic nephritis, complicated by a probable tuberculosis of the kidney. There were no indications of involvement of the bladder. Vesical irritability, pain, and tenderness were altogether absent.

Although nothing was to be hoped for from a more exact knowledge, the patient acquiescing, Dr. C. P. Noble's co-operation was obtained to make an inspection of the bladder and to attempt to catheterize the ureters, in order to determine the extent of the tubercular involvement. On cystoscopic examination the bladder was found healthy. Catheterization of the ureters was attended with such difficulty, because of the very tight hymen, that the attempt was, for this reason, abandoned; and especially because, even if the tuberculous process had been found limited to one kidney, an operative procedure was out of the question.

The patient was under almost daily observation from the time she was first seen (October 21, 1894) until the date of her death—about five months later. During this time her symptoms were such as the chronic nephritis and an imperfectly compensated mitral valve lesion could occasion. There were pronounced uræmic symptoms, held in check for several months by

appropriate remedies, but during the two months preceding her death they were totally uncontrollable. Early in February, 1895, she began to fail visibly. She was unable to leave her house. There was pronounced and persistent insomnia and debility. Dyspnœa was the most obtrusive symptom. It occurred in spells, most frequently at night, when they amounted to veritable attacks of orthopnœa. Without apparent cause the respiration would suddenly become accelerated, reaching 50 or 60 per minute, and occasionally higher. This would persist for an hour or more. The attack would then subside, and a condition of comparative comfort would ensue. With these attacks of dyspnœa there was often pronounced pulmonary congestion. In one of these spells, and that ten days before death, the indications were of pulmonary infarction. The patient was suddenly seized, while at rest, with difficult breathing; the respiration quickly ran up to about 70; the face became deathly pale and the extremities cold; there developed a short, hacking cough, with frothy, blood-streaked expectoration. The heart's action was tumultuous. Ammonium carbonate and whiskey were administered by the mouth at frequent intervals, and strychnine given hypodermatically, while oxygen inhalations were maintained and hot poultices applied to the chest. In the course of an hour the attack entirely subsided and the patient fell asleep. Two hours later, when again seen, she was resting comfortably; respirations were 30; the pulse and temperature 100. The heart was overacting, with marked reduplication of the second sound. An area of solidification at the root of the right lung was apparent.

Free dry cupping in the early evening usually tended to prevent the occurrence of the night seizures, and a prompt resort to the same, on the appearance of the dyspnœa, commonly afforded great relief. Oxygen inhalations were steadily used and always with marked benefit.

Without cardiac medicaments of any sort the heart was generally much overacting, with sharp accentuation of the second sound at the apex. High blood-pressure was so usual, even with symptoms which might have been presumed to be caused by imperfect compensation, that these last, such as decided dyspnœa, could not but be regarded as uræmic in character. Free purgation by calomel always relieved, if it did not entirely prevent, the attacks of dyspnœa until toward the end.

Careful daily thermometric observations were made for two months prior to the death of the patient. Previously the temperature had often been taken when the patient was visited during the afternoon or evening. There was then commonly present slight elevation, not amounting usually to over 1½° F. During the two months preceding death the temperature did not exceed 100° F. It was generally 99° about noon, and from 99⅝° to 100° F. between 4 and 6 P.M.

Two months prior to death the stomach became much distended. Vomiting occurred at least once daily. The vomited matter contained no free HCl. When food was present in the stomach the vomit consisted of clear fluid, which a few days before death had a urinous odor. During the last

two weeks of life vomiting was quite incessant, whether food were taken or not. It was not readily controlled by drugs. It was clearly a uræmic sign. The urine during the last month steadily diminished in amount, not exceeding a daily output of 600 c.c. Toward the end the amount fell to 150 c.c., totally without signs of retention in the kidneys. Casts were always found, and in the examinations, made a week or so prior to death, erythrocytes were present in some amount in addition to the pus-cells. High blood-pressure was maintained up to a day or so before death. The heart showed no signs of failure, being perfectly regular in action an hour or so before dissolution. It continued overacting, with accentuation of the second sound at the apex. The systolic murmur could be heard only inconstantly during the last two weeks of life. For several days before death she vomited continually, and was stuporous. During the last two days she was comatose; the respirations were irregular, and generally did not average over twelve per minute.

The *necropsy* was performed (by Dr. A. O. J. Kelly) seventy-two hours after death. The body was that of a fairly-well developed female; panniculus adiposus slight; the muscular tissues somewhat atrophic. The natural appearances of the tissues and organs of the body were somewhat disturbed, particularly in the direction of excessive dryness, and the serous cavities more or less filled with the embalming fluid. The thoracic and abdominal viscera had their normal positions. The left pleural cavity contained turbid red fluid. The visceral pleura was firmly adherent to the costal pleura posteriorly and below and to the diaphragmatic pleura. Except some slight deficiency of tissue at the edges, the left lung was normal. There were no evidences of tubercular deposits. The right pleural cavity contained also turbid red fluid. The two layers of the pleura were adherent posteriorly and below. The upper and middle lobes of the right lung were normal. The lower lobe was rather dense and heavy, but contained air. There were absolutely no evidences of tuberculosis in the lungs. The pericardium contained about 10 c.c. of clear serum. The heart was much enlarged, the wall of the left ventricle being twice its usual thickness. On the posterior mitral leaflet there was a small islet of thickening. The tricuspid valve leaflets, as far as could be told, appeared normal; the specimen, however, showed such decided post-mortem changes that it was impossible to speak positively concerning this. The aortic and pulmonary leaflets were normal. The omentum was normal. The liver was of about normal size; its capsule was normal. On section, the centres of the acini were reddish-brown, the periphery more yellowish. The gall-bladder was normal. The spleen was somewhat increased in size and rather dense. On section, it was smooth, dark reddish-brown in color, and showed its capsule and trabeculæ thickened. The stomach, pylorus, duodenum, appendix, cæcum, large and small intestines were normal. The left kidney was of about normal size, but denser than normal. Its capsule was here and there somewhat adherent. The surface was mottled in appearance, of a general grayish-red hue, with a few yellowish points alternating with dark-reddish spots. On section the cortex was normal or slightly

Kidney in the case of Mrs. J. H. K.

increased in thickness. There were yellowish-gray striations, with here and there distinct spots of dark reddish-brown color. The left kidney had two ureters, both healthy. One was smaller than the other, and they joined just prior to their entry into the bladder. The right presented the same general characteristics as the left, save as concerns the pelvis. This was dilated and contained pus. The surface of the pelvis was studded with about a dozen and a half or more of small miliary tubercles of grayish-white and yellowish color. The ureter was normal. The bladder was healthy. It contained a small amount of pus from the kidney pelvis. The uterus was somewhat atrophic. Attached to its right cornu was a pedunculated fibroid, the size of a goose-egg; on its anterior surface, to the right of the median line, was a calcareous fibroid the size of a small chestnut. The tubes appeared a trifle thickened, but otherwise normal. The ovaries were atrophic. The retro-peritoneal glands were normal.

The pathological diagnosis was chronic diffuse nephritis with tuberculous pyelitis of the right kidney; hypertrophy of the heart; chronic induration of the spleen; nutmeg liver.

A subsequent examination of the pus from the pelvis of the kidney and of that found in the bladder (originally from the pelvis) disclosed the presence of tubercle bacilli in both. A microscopic examination of the diseased organs confirmed the above macroscopic diagnosis. No disease of the Fallopian tubes could be detected. (See Plate I.)

This case, therefore, of primary miliary tuberculosis of the kidney is presented as an instance of that rare class of cases characterized by the development of miliary tubercles in but one kidney and unassociated with any other discoverable tuberculous lesion in the body. It is also to be noted that this variety of tuberculosis of the kidney does not of necessity progress to the ordinary or caseous form of primary disease, but that it rather continues as it originates.

Quite distinct from the unusual primary miliary tuberculosis of the kidney is the other and much more common variety of primary tuberculosis of the kidney, the caseous variety. As the miliary, so also the caseous variety commences in that portion of the kidney to which the bacilli gain access and are arrested. The primary focus is usually in or near the renal papillæ, and from here the process spreads to the surrounding renal parenchyma. When the process does not begin in the papillæ it may commence in the calices or in the pelvis of the kidney, or in the cortex; and it is quite probable the cortex is much more frequently the point of departure for the general involvement of the kidney than is commonly assumed. Again, it sometimes seems that, as in the miliary variety, the regions

supplied by one branch of the renal artery were, for a time at least, alone affected. The initial lesion being, therefore, usually situated in the papillæ, it is a matter of but a short time until the tubercular virus, partly by way of the bloodvessels, partly by way of the lymphatics, and partly, also, by way of the uriniferous tubules, is carried within the substance of the kidney, setting up, at its place of lodgement, lesions similar to those whence it came. The process commences by the formation of grayish nodules, which differ from the formations of miliary tuberculosis in their much greater size and by the tendency they early manifest to undergo caseous necroses. So marked is this tendency that shortly after its formation in the conglomerate tubercle isolated tubercles are frequently impossible of detection. Thus an irregular, softened area is soon formed, and this, by a process of peripheral extension, gradually spreads in all directions, especially toward the cortex. Being near to the pelvis, this latter soon becomes implicated in the process. The mucous membrane of it may be the seat of either an eruption of miliary tubercles or of a diffuse tuberculous infiltration. Thus, by an increase in the size of an initial lesion, and by the development of other tuberculous foci, the result of added infection, there occurs a time when the caseous areas spreading toward the periphery implicate the medulla, finally the cortex, and may eventually involve a major portion of the organ. As these areas degenerate the kidney becomes the seat of irregular, roundish cavities if the necroses occur within the parenchyma of the organ, or of a tuberculous, ulcerating surface if the pelvis be affected. If the process originate in the cortex, as it may, the focus, degenerating, gives rise to a closed cavity. These and other caseous masses within the parenchyma of the organ as they become necrotic are apt to assume a form corresponding to the papillæ—that is, they become pyriform, and, reaching the pelvis, they rupture into it. This latter, thus originally encroached upon by the new tissue-formation, increases in size as the necrotic material is discharged into it. It communicates with the several cavities, and one may speak of a phthisis renalis tuberculosa. The various cavities are at first separated from each other by walls containing more or less renal parenchyma. Sooner or later these also are involved, become necrotic, break down, and are removed. The kidney is thus converted into a many-cham-

bered cyst, with established communications between the various cavities. These, reaching toward the periphery, are often visible from the exterior, and give to the organ a somewhat bosselated appearance. That tissue nearest the centre of the necrotic area is yellowish in color, indicating that here the disease is more advanced and the process degenerating, while that toward the periphery is grayish and of newer formation. Microscopically, the caseous masses often fail to reveal any vestiges of tubercular formation, justifying the term caseous inflammation or nephritis caseosa, especially as the uriniferous tubules are apt to be found filled with caseous material (proliferated, degenerated, and caseous epithelium). At the periphery of the caseous masses the nodular make-up of the new tissue-formation is, however, readily recognized, and epithelial cells, giant-cells, round-cell infiltration, and tubercle bacilli are encountered. These latter are often found in greatest number within the uriniferous tubules, *via* which, as already remarked, the process may spread. The process may also attack a minute bloodvessel, and the caseous matter rupturing into it thus give rise to extension. The glomeruli are often the seat of round-cell infiltration. Late in the course of the disease the appearance of the kidney is quite characteristic. It has entirely or in part become converted into a many-chambered sac, the various cavities of which vary much in size and in number, ten to fifteen not infrequently being encountered in one kidney. They usually communicate with themselves and with the pelvis of the kidney—the former by implication and subsequent caseation of the septa; the latter by the rupture into the pelvis of the degenerated foci. So extensive may be the destruction of the kidney substance that the septa may be entirely wanting and the kidney may have been converted into one huge sac, the wall of which will vary much in thickness in different parts. On their inner aspect these cavities are rough and irregular and are covered with a caseous material of a dirty grayish color. Occasionally one detects appearances suggestive of attempts at healing of a pulmonary tuberculous focus, in the shape of calcareous plates or granules. The contents of these cavities much resemble putty. The cyst or cavity contents are usually of dirty grayish color. With admixture of much pus they approach a yellowish color, and blood bestows a reddish tint. Not rarely they are sero-sanguinolent. The cyst con-

tents are of a urinous odor and always deposit a sediment. This latter consists of a cheesy detritus, partially degenerated tubercles, caseous renal tissue, blood, pus, triple phosphates; less frequently calcareous matter, phosphate and carbonate of lime, and cholesterin, etc.

On external examination the kidney may appear to be of about normal size; or, with preservation of its configuration, it may be moderately or greatly increased in size. This latter is usually observed late in the course of the disease, and is induced by a pyonephrosis sequential to blocking of the ureter. This leads to distention and sacculation of the organ, and finally to complete destruction of all secreting structure. Should one organ only be involved, the drying up of the fluid contents leads to an atrophic kidney containing inspissated, putty-like masses; or, rarely, one kidney may present an appearance akin to this, while the other may be of about normal size or greatly distended—the seat of a pyonephrosis. The kidney is quite adherent and greatly thickened. Not rarely it forms intimate associations with the perirenal fat—that is, it is well-nigh impossible to separate or distinguish them.

Associated with the disease of the kidney substance, the pelvis usually manifests lesions peculiar to itself. As already alluded to, it may constitute the seat of primary infection. It may thus be affected prior to, simultaneously with, or subsequent to, the kidney lesion. It may be the seat of miliary tubercles, tubercular infiltration, or both. Originally encroached upon by the increase in size of the kidney by the developing tubercular new formation, as the caseous foci discharge their contents into it, it augments in volume. It is usually covered with a dirty grayish, putty-like or membranous-like formation, under which or between portions of which tubercular ulcerations are common. Late in the course of the affection, with extensive destruction of the kidney and free communication between the cavities and the pelvis, the limits of the latter are usually not determinable. The pelvis is usually dilated from obstruction of the ureter, and contains substances similar to those detailed as occurring on the kidney cavities.

The ureter presents lesions the counterpart of those found in the pelvis. On external examination it may appear distended, but upon section its walls are usually found thickened and its lumen decreased.

Its inner surface is irregularly ulcerated and covered with a dirty-grayish or yellowish, membranous-like formation. This, with the thickening of the submucous coat, leads to constriction or obliteration of the lumen and the conversion of the ureter into a more or less rigid tube. Obstruction of the ureter may also be induced by arrested blood-clots or caseous material, be it masses or shreds. The obstruction leads to distention and thinning of the parts above, and consequent dilatation of the pelvis and renal cavities.

When the destruction of the renal parenchyma is well advanced, and the walls of the cavities have become thinned, perforation not infrequently ensues, leading to the formation of perirenal abscesses. These have also been said to be due to lymphatic infection; but this, if it occurs, must be very rare. In general, these abscesses present characteristics similar to those of the renal cavities. They are often made up of irregular, communicating cavities containing material similar to that in the kidney. They extend in all directions, and, though of slow development, they may make their way through the diaphragm into the iliac fossa, or they may even perforate externally.

The bladder is usually contracted, and has thickened walls depending upon hypertrophy of the muscularis and induration of the mucous membrane, which may be tuberculous or not. The mucous membrane may be the seat of an eruption of miliary tubercles or of more extensive tubercular infiltration or ulceration, particularly at the trigone and fundus. But not uncommonly the tuberculous process terminates at the ureteral orifice of the bladder. It must be mentioned, however, that it has been asserted that the microscope will sometimes reveal tuberculous lesions of the bladder when to the naked eye the viscus appeared healthy.

A marked characteristic of this variety of primary tuberculosis of the kidney is the tendency for the other portions of the genito-urinary tract to be implicated in the process—whence the common designation, uro-genital tuberculosis. Not rarely both kidneys are found diseased—one, however, usually in a more advanced stage of the disorder than the other. The involvement of the ureter and the bladder have already been referred to. There are often found tubercular lesions of the testicle, epididymis, vas deferens, or prostate. At times the seminal vesicles alone may be affected. In the female the Fallopian tubes may be the starting-point of a uro-genital

tuberculosis, but at the same time an uncomplicated urinary tuberculosis may occur. These associations of the renal disease, while not always found, still have important pathological, clinical, and therapeutical bearings.

The mode of infection in these cases is a most interesting problem, and has long been a fruitful source of discussion. In many cases it is exceedingly obscure, and cannot be removed from the realms of pure conjecture. Three possibilities only suggest themselves: 1. Hæmatogenic infection. 2. Ascending infection from the lower urinary tract, either by means of the urine, through the spread of the disease along the ureter, or by the conveyance of the virus through the lymphatics. 3. Extension from similar processes of neighboring organs. The latter, if it occur at all, must be a very rare mode of infection. The kidney is notably exempted from participation in the disease of neighboring structures, as of the vertebræ, adrenals, etc. The capsule probably acts as a protecting membrane; witness the non-implication of the kidneys in tuberculosis of the suprarenal bodies, even when the latter, as it sometimes does, give rise to a perinephritic abscess. The mode of infection must, therefore, be hæmatogenic, or the kidney must become implicated by an extension of the process from below upward. There is clear evidence in support of both views. We thus recognize that the caseous variety of tuberculosis of the kidney may be either a primary or a secondary affection, and that there may occur both an ascending and a descending tuberculous infection of the genito-urinary tract; and, further, we must allow that various parts of the tract may be simultaneously involved. There can be no doubt that in the case reported by us the infection was hæmatogenic, and this is also doubtlessly the most frequent mode of infection in the ordinary primary caseous or local tuberculosis of the kidney, there subsequently ensuing a descending infection of other parts of the lower genito-urinary tract. It thus appears evident that a primary tuberculosis of the kidney, similarly as primary tuberculosis of the bones and lymph-glands, may occur by hæmatogenic infection without any demonstrable tuberculous lesion in any other part of the body. Of course, one can hardly exclude the possible presence of a small tuberculous focus which may have eluded detection. The interesting question under these circumstances is, in what manner do the bacilli gain access to

the body and enter the bloodvessels? One naturally has recourse to the experiments which serve to prove that the bacilli may enter the body without setting up lesions at the port of entry. We further recall the symptomless course of many unsuspected cases of tuberculosis of various structures—the tonsils, bronchial and cervical lymphatic glands. Infection of the latter, it appears from some recent investigations, may occur by means of totally latent tuberculosis of the teeth. Again, the tubercle bacilli have been demonstrated in the renal glomeruli before any cellular exudate has occurred. But, despite various facts and theories, the mode of infection of some cases of primary tuberculosis, not only of the kidney, but also of other organs, is exceedingly obscure. At times the question is impossible of solution.

While from the appearances of a kidney, removed either post mortem or by operation, it is frequently relatively easy to determine the route of infection, in a not inconsiderable proportion of cases this is a matter of very great difficulty, and is at times impossible. Disseminated or secondary miliary tuberculosis, and the primary form of miliary tuberculosis such as we report, are readily recognized as instances of hæmatogenic infection. When, however, more or less of the entire uro-genital tract is affected, it requires a careful consideration of the relative stages of the various lesions found at the more remote points of the disease to determine the route of infection; to determine whether or not the general implication be an instance of descending or of ascending infection, in which latter case, of course, we can but speak of a secondary involvement of the kidney. A more advanced stage of the disease about the trigone or fundus of the bladder, for instance, and relatively little implication of the kidney, and that limited to the pelvis or papillæ, would be clear evidence of an ascending infection. Again, extensive destruction of the kidney, more especially toward the cortex, with some slight involvement of the ureter and healthy bladder, is sufficiently characteristic of the descending variety of the infection. Attention might here be drawn to the fact that whereas a few years ago the generally accepted notion was that the kidney involvement in caseous tuberculosis was usually an instance of ascending infection from the lower uro-genital tract, the trend of recent opinion is that the primary focus is commonly situated in the kidney, the other

organs of the genito-urinary system becoming secondarily involved. Not rarely both kidneys are affected, though one is generally found to be in a more advanced state of disease than the other. This bilateral implication may be the result of simultaneous infection, or, as is most probable, usually the second kidney has become infected from the first by a descending and subsequent infection. The tuberculous disease of one kidney gives rise to a descending infection of its ureter, and finally the bladder, the mucous membrane of which, especially that about the trigone and fundus, becomes the seat of miliary tubercles or becomes infiltrated or ulcerated. The ureter of the healthy kidney becomes diseased and its mucous membrane thickened. This results in obstruction of its lumen and consequent hydronephrosis, which shortly becomes purulent. Thus, the tubercular infection is presented to the pelvis of the healthy kidney, and it soon succumbs to the attacks of the morbific agents. It is also believed that an urethral obstruction occasioning retention of urine may result in such disease of the second kidney, and this sometimes without affecting the bladder, the mucous membrane of which is notably resistent to the injurious influences of diseased germs.

Primary tuberculosis of the kidney may occur at any age, but is more frequent in adult life and old age. Hamill, who has recently made a very exhaustive study of the disease as it appears in early life, and who has reported one of the youngest cases on record—a child aged seven months (*International Medical Magazine*, 1896)—remarks that it "is relatively uncommon in childhood and exceedingly rare in infancy." In the young the conditions are probably not identical with those found in later life. It appears that more males are affected than females. The etiological factors are those of tuberculosis in general.

As already remarked, disseminated miliary tuberculosis of the kidney may not and usually does not give rise to any special symptoms, being but part of a general process. It is also true that primary miliary tuberculosis, as well as the ordinary variety of primary or caseous tuberculosis of the kidney, may persist for a considerable time without exhibiting any clinical manifestations of its presence. Rosenstein is authority for the statement that symptoms develop only when the mucous membrane of the pelvis and calices or ureter become the seat of inflammation, or when the caseous tubercles rup-

ture into the pelvis; but, as evidenced by the case reported by us, even the implication of the mucous membrane of the pelvis may not give rise to any obtrusive indications. Rosenstein further asserts that the initial symptom of all cases (at least in all of the considerable number observed by him) was dysuria.

Laroche, a recent observer, feels justified in dividing all cases, according to their initial manifestations, into three classes—those which commence with hæmaturia, those which commence with pain, and those which commence with vesical symptoms; but, as further instanced by the case reported by us and by others, the condition may not be suspected until the accidental discovery of pus in the urine, during a careful examination of the renal secretion, suggests to the examiner the wisdom of examining the sediment for tubercle bacilli.

The symptoms which, developing, attract the attention of the patient, are usually, in the beginning, either lumbar pain, turbid urine, hæmaturia, or, what the patient is more likely to observe, frequent and painful urination and hæmaturia. Any of these may occur alone, or there may be various combinations. Guyon was wont to refer to pus in the urine, frequent and painful micturition, as the common symptomatic triad of urinary tuberculosis.

Lumbar pain may be present alone, and may be either spontaneous or provoked. The spontaneous pain may be very slight, amounting only to a so-called loin tire, or it may be very severe. It is usually limited to the lumbar region, and is present on or at least more severe on the diseased side. It is not ameliorated by repose nor aggravated by movement. Sometimes the pain is lancinating, and even when so it may be confined to the lumbar region, or it may exhibit radiations in the direction of the ureter or into the testicle. Again, veritable crises appear at irregular intervals. They are of variable intensity and duration, and usually develop without manifest cause. They much resemble attacks of nephritic colic. The pain is generally aggravated by pressure—that is, by an examination of the renal region; but pain provoked only by an examination, being otherwise absent, must be a rare indication of primary tuberculosis of the kidney.

Vesical and urinary symptoms have for a long time been known to accompany various diseases of the kidney, despite the integrity of

the bladder, and in primary tuberculosis of the kidney they are common. Frequent and painful micturition is a common initial symptom. At times pain may be intense, and situated at the neck of the bladder and accompanied by aggravated vesical tenesmus. Frequent urination, by night as well as by day, is often the first obtrusive symptom, even before the appearance of pus or blood appreciable to the eye in the urine. It often coexists without painful urination, so that the patient may alone complain of the mere annoyance of the great frequency of the act of urinating.

The presence of blood in the urine, often only to be detected microscopically, is probably the most frequent initial symptom, and may be present for a long time without any other manifestation of the disorder. Its production is readily accounted for by the fact that the bacilli, gaining access to the glomeruli, there set up a congestion which speedily progresses to rupture of the bloodvessels and consequent blood in the urine. It not only occurs early, but may be passed also during all stages of the affection. Hæmaturia varies much in amount, and usually occurs without provocation—that is, it develops as it also ceases—spontaneously. The time of its occurrence and its amount are uninfluenced by movement or repose. It may be accompanied by severe pain, but even when profuse it is generally painless.

An examination of the kidney region often affords important diagnostic data in a suspected case. A kidney increased in size and painful is valuable evidence of the condition. The kidney unaffected with the tubercular process may be enlarged from compensatory hypertrophy, but it is not painful. On percussion the area of kidney dulness is found enlarged; to facilitate the delimitation of this area the employment of auscultatory percussion by means of the binaural stethoscope or the phonendoscope may be of value. Careful and thorough bimanual palpation alone will commonly enable us to distinguish enlargement, especially when the right kidney is involved. A kidney increased in size and painful may be observed very early in the disease. Later there may be bulging of the loin and a tumor in the abdomen. This latter, depending upon the state of the pathological processes in the kidney, varies much in size and other characteristics. The general conformation of the kidney is usually retained, but the tumor-mass may be very voluminous from

a pyonephrosis consequent upon an obstruction of the ureter. If the several renal cavities reach the surface of the organ, the tumor-mass may feel bosselated. It may be resistant to pressure—that is, it may be hard or firm—or it may be elastic or fluctuating. It may be so exquisitely painful to pressure that a satisfactory examination cannot be accomplished without an anæsthetic, and this is usually contraindicated.

The most important symptom of the disease is the specific alteration of the urine. The characteristics of the urine are the reflexion of the renal condition, and when a direct examination of the organ leads to indefinite results an investigation of its secretion alone furnishes positive signs. The urine may vary in amount. In the initial stages polyuria with frequent urination may be the sole symptom. Later the quantity of urine depends in a great measure upon the state of the renal parenchyma. With destruction of the secretory tissue the urine diminishes in amount, but with an associated cirrhosis of the other kidney polyuria would be usual. The polyuria is frequently intermittent, and is commonly excessive after the removal of an obstructing particle from the ureter. The specific gravity of the urine is generally normal or somewhat subnormal. With marked polyuria it is of course very low. The reaction is acid. The urine is usually turbid when voided, but is not infrequently clear, and this is sometimes said to be especially the case during the painful crises, following which marked turbidity supervenes. Again, after turbid urine has been voided for a while it may suddenly clear and remain without sediment for some time. A sediment is sometimes deposited immediately upon the urine being voided; again it does not deposit for some little time. This consists of pus, blood, epithelium (occasionally casts), connective tissue, and elastic fibres and detritus. Cholesterin plates and crystals of calcium carbonate, phosphate, and oxalate are sometimes found. The quantity of pus is variable, as is also the albumin, which, with the presence of pus, is of course always found, and in amount depends upon the pus and blood. With parenchymatous disease of either the tuberculous or the other kidney the percentage of albumin increases. Tubercle bacilli are always demonstrable in the sediment, sometimes in the course of the case.

As the disease progresses constitutional symptoms develop, but it

is remarkable how extensive the kidney disease may become before they manifest themselves. The patient, from the first somewhat pallid, with perhaps little loss in flesh, grows gradually weak and finally emaciated. There is present anorexia, with increasing anæmia and an evening rise in temperature. Eventually the case passes into a condition of decided cachexia, and death may thus occur without extension of the tuberculous process beyond the genito-urinary tract.

As illustrating how insidious in onset and symptomless in at least a portion of its course tuberculosis of the kidney may be, the following case, occurring in the private practice of one of us (Dr. Stewart), is of considerable interest. In this, with absence of the commonly observed frequent urination and hæmaturia (at least microscopic), the first indication of any departure from health was the accidental discovery of pyuria:

The case is that of W. R. S., dentist, aged thirty years; weight, 145 pounds; family history good. Although he had never been robust, his health had always been fair. He was subject to "colds." He consulted Dr. Stewart for the first time in October, 1896, for the purpose of ascertaining the cause of the presence of albumin in his urine. Two and a half years before he had taken out an insurance policy in a prominent company. At that time no abnormalities of the urine were noted. Six months before he came under observation he was insured in another and less prominent company. At this time, also, an examination of his urine was made, although by an examiner of less note than the first one. Shortly before consulting Dr. Stewart the patient desired to increase the amount of his life-insurance. He was told by the examiner for the company first referred to that it would be impossible at that time, as his urine contained albumin. It was on account of this that he consulted Dr. Stewart. A specimen of urine voided for examination was found to contain considerable pus, with albumin in amount only to be accounted for by the presence of the pus. The patient now recalled that for several months past the urine was commonly turbid on voiding. To this he had not before attached significance. The patient's general health was good. In appearance, although well nourished, he was somewhat pallid. An examination of his blood disclosed a minor grade of anæmia—hæmoglobin, 65 per cent.; erythrocytes, 4,000,000; no leucocytosis. There had been no loss of flesh, and his health, save for occasional slight attacks of bronchitis, had always been good. Some five years previously he had had more or less bladder irritability, and this had persisted as a quite constant symptom for perhaps two years. The indications pointed to a mild chronic cystitis, for the development of which he could offer no explanation. He had not had gonorrhœa. The bladder trouble, which at no time had been more than

slight, had been entirely dissipated about three years before he came under observation, by the use for a short time of suppositories consisting of belladonna, iodoform, and cocaine. His health since had been very good. He had taken a great deal of outdoor exercise, chiefly awheel. He was absolutely symptomless when seen for the first time for his present ailment. Irritability of the bladder was entirely absent, and has been persistently so for the past three years. He never rose at night to urinate, and rarely passed water over three times during the twenty-four hours. Hæmaturia had never occurred to his knowledge. The testicles and their appendages were to all appearances normal. There was no tenderness about the neck or other palpable portions of the bladder. The kidneys were not palpable, and tenderness in the region of their location, even on firm pressure, was absent. The lungs and heart were normal.

The case was regarded as one of probable tuberculosis of the kidney, and a search in the urine for the tubercle bacilli was at once instituted. As a matter of routine, specimens of the urine were examined in Dr. Stewart's laboratory, both by himself and Dr. A. A. Ghriskey, systematically twice weekly, for seven weeks before tubercle bacilli were found. They were at last discovered by Dr. Ghriskey after their detection had almost been despaired of. At the end of this time in the first mount made, in one field only, a very large number were found in good-sized clumps and others isolated. No other fields contained them. Evidently, those encountered were from a small shred of tubercle which had escaped into the urine.

The amount of urine voided, measured over several days at intervals, was found to run constantly between 1200 and 1500 c.c. Although turbid on voiding, it always became clear on standing. Specimens of the day's urine deposited a considerable sediment, consisting solely of pus. That passed on arising in the morning commonly contained pus in much less amount. The urine was always of acid reaction, of normal color and gravity, and the twenty-four hours' output habitually showed normal urea for body-weight and diet. Albumin was present only proportionate to the amount of pus, from which it was evidently derived. Microscopically, pus-cells abounded. Erythrocytes and bladder epithelium were not noted. Casts in the many examinations made were never encountered.

Thermometric observations, made twice daily in the case for over a month, showed no afternoon or evening rise of more than a half degree.

A diagnosis of presumed tuberculosis of the pelvis of the kidney was made and the case maintained under steady observation. During this time, as narrated, a search for tubercle bacilli was being made. The treatment consisted of a nutritious diet, fresh air, and a good deal of rest in recumbency throughout the day. Guaiacol benzoinate was employed internally, although not with any expectancy of benefit. Rather large doses were at first taken, resulting in mild toxic symptoms, the chief of which was a tendency to persistent chilliness, which ceased on discontinuance of the remedy. During the time it was being taken in full doses, on undue exposure to wet and colds, a chill occurred, followed by soreness in the region of the left kidney. When seen, the second day after this was experienced, there had been some diminution in the amount of urine voided (the quantity at this time not being measured). There was also a perceptible though slight fulness evident in the loin anteriorly and laterally. The loin was somewhat tender on pressure. This was the only indication of hydronephrosis that had ever occurred. It was not repeated while he was under observation. Drinking freely of hot lithia water, and the employment of dry cups, followed by a poultice, caused a prompt subsidence of the symptoms.

The patient was under observation about three months, and, although now no longer under Dr. Stewart's care, is still occasionally seen. Immediately on finding the tubercle bacilli in the urine it was urged on the patient to submit to a cystoscopic examination. The intention was to make an inspection of the bladder and to attempt catheterization of the ureters, in order to determine if the process, as was supposed, was limited to one kidney. If this suspicion were found confirmed, surgical interference was contemplated. But to the cystoscopic examination the patient would not consent, although the necessity of it was persistently laid before him, he being given to understand that no remedy could be curative of his condition. For this reason he consulted another physician, who held out to him greater promise of relief by drugs.

In this case the indications strongly pointed to a tuberculous pyelitis of one kidney, presumably the left. The ailment was probably of recent origin. It was unaccompanied by any indication of genito-urinary implication. The bladder symptoms, which were

present several years previously, were of themselves highly suggestive, but should not be accorded undue weight, as they were not accompanied by any signs of renal derangement, which latter did not develop until three years after the subsidence of the symptoms of vesical irritation. During this time the man had enjoyed good general health, and two examinations of his urine for life-insurance had failed to disclose any indications of abnormality.

The diagnosis of primary tuberculosis of the kidney, particularly in the early stages, is frequently a matter of the greatest difficulty. The diagnosis may be at times most positive and again most uncertain. As in the two cases reported by us, the disorder may develop entirely without manifest symptoms. In the first case the tuberculous disease became engrafted upon a kidney the seat of chronic inflammation, and it was the presence of pus that alone suggested the wisdom of examining the sediment for tubercle bacilli. In the second case the first indication of abnormality was the accidental discovery of albumin in the urine when the patient desired an increase in his life-insurance. The albumin was found dependent upon pus, and this again led to the examination of the sediment for tubercle bacilli. In this case it was only the persistent and frequently repeated examinations for a period of almost two months that were finally rewarded by their detection. We cannot, therefore, too strongly accentuate the suggestiveness of the presence of pus—even in very small amount—in acid urine in the diagnosis. The negative result of the examination of the urinary sediment for bacilli is not evidence of the freedom from the tuberculous disease. The examinations must be frequently and persistently made. The positive evidence only is of certain diagnostic importance. We confidently believe that the systematic, careful, persistent, and frequently repeated examination of the sediment of urine containing pus, even in small (microscopic) amount, would more often permit of the recognition of the class of cases to which we allude. Rarely the urine may not be acid. It may have been rendered alkaline by some complicating condition, such as a cystitis induced by the employment of an unclean catheter. In a case of Dr. Stewart's, in which both kidneys were involved in the tuberculous process and were converted into mere pus-sacs, the urine had remained steadily acid until the employment of cystoscopy, sub-

sequent to operation on one of the kidneys, induced a cystitis, with subsequent ammoniacal fermentation.

The absolutely diagnostic sign of renal tuberculosis is the discovery of the tubercle bacillus. Care must be taken not to confound the smegma bacillus with the tubercle bacillus—an error which has led to the removal of a kidney the subject of calculus only, but presumably the seat of tuberculosis. Although the staining peculiarities of these bacilli are in many respects alike, the arrangement of tubercle bacilli into masses and groups, and this especially occurs in tuberculosis of the uro-genital tract, is quite distinctive. The differential characteristics existing between the smegma and the tubercle bacilli have been especially studied by Grethe and von Leyden. The smegma bacilli are more readily decolorized by acidulated alcohol, losing their stain in two minutes, while tubercle bacilli do not. The smegma bacilli do not stain by Gram's method; the tubercle bacilli do. Grethe advises staining a cover-slip preparation first with carbol fuchsin, in the ordinary manner, and then with a concentrated alcoholic solution of methylene-blue. The smegma bacillus is thus stained blue, and is in marked contrast to the tubercle bacillus, the red color of which is not interfered with. When, after persistent search, the tubercle bacilli cannot be detected in the sediment, small flakes of tissue being especially looked for as most likely to contain them, the question of diagnosis may be settled by injecting some of the sediment into the anterior chamber of the eye or into the peritoneal or pleural cavity of a rabbit or guinea-pig. Of less value is gelatin or other plate-cultures from the pus. The discovery of connective tissue and elastic fibres in the sediment merits our careful consideration. While not diagnostic of tuberculous disease of the kidney, their presence still points to some extensive destructive disorder in the kidney, and this is usually tuberculous or dependent upon a calculus. The suggestiveness of these is greatly increased when they are associated with degenerated particles of tubercles, which are so common in the urine and which generally appear as granular, amorphous masses. The diagnosis is further confirmed should there be present hæmaturia and indications of enlarged and painful kidney, lumbar pain, and vesical irritability.

The evening elevation of the temperature, as insisted upon by

Rosenstein, cannot be so distinctive and essential a symptom as he would have us believe. In our second case the evening rise did not amount to more than the normal elevation, and in the first case the elevation that occurred might be regarded as dependent upon the other conditions evident. However, an evening rise of the temperature in association with acid urine containing pus is very suspicious of tuberculous disease. Confirming one's apprehension of a possible tuberculous disorder of the kidney is the discovery of similar disease of other parts of the genito-urinary system, as of the testicle, epididymis, vas deferens, seminal vesicles, prostate, bladder, ureter, and, in the female, the Fallopian tubes.

The presence of persistent lumbar pain, pyuria, hæmaturia, and vesical symptoms all call for a careful investigation of the kidney. The impartial observer will hardly mistake the lumbar pain for a lumbago; nor should a pyuria with vesical symptoms be too long referred to a catarrh of the bladder. Frequent micturition alone or accompanied by hæmaturia, but without lumbar pain or other symptoms, is in itself very suspicious.

The distinction between calculous pyelitis or pyonephrosis and tuberculous disease is at times a matter of some difficulty. Vesical irritability is common to both conditions, but the lumbar pain of calculus is usually of a duller, much more persistent character, is aggravated by motion, and is associated with attacks of renal colic in which the pain is agonizing and radiates into the lower genitalia and into the thigh. When such attacks accompany tuberculous disease they are generally much less intense. Hæmaturia is more severe in renal stone, and is often induced by exertion. Enlargement of the kidney is not so common, and only occurs when the stone becomes impacted in the pelvis or in the ureter, and this is usually late in the course of the disease. There then ensues a hydro- or pyonephrosis. The urine is usually highly acid in calculous disease, with a specific gravity normal or above; it contains, if the calculus be of uric-acid formation, usually an abundance of crystals of the same; if of calcium oxalate, similar crystals are likely to be present in excess. Casts are less frequent than in tuberculous disease, and the bacilli are, of course, not encountered. While good general health may be maintained for a long time despite the tuberculous involvement of the kidney, still the patient is more apt to

show deterioration sooner with tuberculous disease than he is with renal calculus. For an exceedingly long time between the attacks of renal colic the patient's general health is excellent. In tuberculous disease not infrequently there rather early develop some emaciation, anæmia, night-sweats, loss of appetite, etc. The symptoms are sometimes indicative of vesical calculus, but from this the employment of a sound or the cystoscopic examination of the bladder readily differentiates. Both the renal and the vesical calculi may further be excluded by the results of a Roentgen ray skiagraph. Malignant disease of the kidney is usually easily eliminated from the possibilities. Frequent urination and hæmaturia are the only urinary symptoms common to both conditions. But hæmaturia may be absent in malignant disease, and, if present, is apt to be abundant. The tumor generally grows very rapidly, renders the kidney firm to the touch, bosselated, and may lead to distortion of its shape. Sarcoma is the most frequent tumor, and it is in children that confusion is more likely to arise.

In all cases, and especially in women, in which such examination is now a matter of comparative ease by the employment of the improved methods of Howard Kelly, a cystoscopic inspection of the bladder, and especially of the ureteral orifices, should be early carried out. In women, in addition, catheterization of the ureters is a matter of little or no difficulty, and may be essential to determine, by an examination of the urine from each kidney, the question of single or double involvement. Meyer holds that in a suspected case the use of the cystoscope will determine the diagnosis, even though repeated search in the urine for tubercle bacilli has been resultless.

Meyer (*Medical News*, March 1, 1896, and May 1, 1897) states that with involvement of but one kidney, by the cystoscope a permanently normal vesical mucous surface is seen with a single healthy ureteral opening. The orifice of the other ureter is, however, injected. "A number of circumscribed, clearly defined, inflamed areas of mucous membrane can be seen between it and the slightly hyperæmic trigonum, leaving the interposed tissue unchanged in appearance." No other disease of the kidney or bladder presents a similar cystoscopic appearance, in Meyer's opinion.

The case may, however, be encountered before such a cystoscopic picture is evident. In any event, in addition to cystoscopic exami-

nation, catheterization of both ureters, when possible, should be accomplished to obtain separate specimens of urine. In its performance the chances of infection of the yet healthy kidney must be thought of and precautions taken to minimize such an accident.

Catheterization of the ureters in the male is, unfortunately, attended with great difficulty, and has been accomplished by few, either in this country or abroad. By these it has been done sufficiently often to indicate that, although not easy of accomplishment, it is at least, in experienced hands, practicable.

The prognosis in the vast majority of cases without operative interference is absolutely fatal. One can think of the possibility of the disease being limited to one kidney, the substance of which wastes and finally becomes the seat of "clinical but not anatomical recovery," while the other kidney remains intact. But such a possibility is very remote. The disease lasts for from six months to two or three years, as a rule, though instances of cases of much longer duration have been recorded. Death follows from cachexia, or it may be due rarely to uræmia, from associated chronic nephritis, as in the case related by us.

The treatment of primary tuberculosis of the kidney, of whatever variety, is distinctly surgical; the employment of tuberculin, the recently vaunted nucleins, and drugs, such as guaiacol benzoinate, being without permanent benefit.

The surgical management of the case will not be here considered. Of the greatest practical importance is it, by careful hygienic and medical means, to place the patient, prior to operation, in as favorable a physical condition as possible, that any latent tuberculous process other than in the kidney, such as in the lungs, be not subsequently stimulated into activity through the depression attending operation.

Theoretically, apart from the ability to directly reach the morbid process and effect its removal, operation, the immediate effects of which are well understood, may be not without benefit on tuberculous lesions elsewhere, in a manner similar to that in which cure often results from mere incision in cases of tuberculous peritonitis. The most plausible explanation of the remarkable results obtained by mere exploratory cœliotomy in cases of tuberculous peritonitis is that of Kischenski (*Centralblatt für Chirurgie*, 1893), who regards

the benefit or cure resulting due to the invariable post-operative leucocytosis. The beneficial effects in peritoneal tuberculosis, although in all probability so resulting, cannot be expected to repeat themselves in the same degree in tuberculous lesions elsewhere, for certain reasons (see, as to this, a paper by Vaughan: "Yeast Nucleinic Acid in Tuberculosis," *Medical News*, March 6, 1897, p. 300); yet much may be expected if the system is well fortified, prior and subsequent to operation, by supportive treatment. In these cases the free administration of preparations of nuclein, especially, as advised by Vaughan for use in general tuberculosis, of yeast nucleinic acid, may be of considerable advantage.

TWO CASES OF BRONCHO-BILIARY FISTULA.

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At the first meeting of this Association, held in 1886, I presented a paper entitled "Notes of a Case of Hepatic Bronchial Fistula." I then gave the history of a patient in whom a complete recovery seemed to have taken place. It is my present intention to describe the further progress of this case, and to give a *résumé* of the literature relating to it, especially that which has appeared during the last ten years.

A brief account of the previous history of the patient as it was recorded in my former paper is necessary to the proper understanding of the case. The following notes were made in the spring of 1887:

S. H., aged thirty-three years, paper-box manufacturer; married; father of two healthy children. Patient is temperate and regular in his habits, and has never suffered from any form of venereal disease. He has had but one illness, which occurred three years ago This attack may have some bearing upon his present condition. He was seized with pain in the region of the gall-bladder, which passed around to the back. He suffered from fever, but had no jaundice. The treatment employed was principally of a palliative character. Hot fomentations were applied locally, and sedatives given. Patient was in bed three weeks, and the attack lasted altogether about six weeks. He complained, however, both before and afterward of pain in the hepatic region. He recovered completely, and remained quite well until the commencement of the illness about to be described. In the latter part of November, 1886, he was seized with coughing and pain in the right hypochondriac region, at a point three inches to the right of the median line, and a little below the margin of the ribs. He was also troubled with nausea and vomiting. The vomited matter had a greenish-yellow transparent appearance. These symptoms began on November 27th and continued until December 2d, when he first saw Dr. Stark, who is his family physician and who attended him during the previous attack. His pulse was then 120; skin hot and dry; countenance flushed and anxious; mouth, nose, and ears stained with the

greenish-yellow matter he had been vomiting. He had had a severe chill during the previous night. Temperature not taken. Treatment: quinine, hydrobromic acid, and compound tincture of camphor.

Dec. 3*d.* On examination of the chest the area of hepatic dulness was found to be much increased, and a pleuritic friction-sound could be distinctly heard immediately below the right nipple. Pain in that region very severe; patient complained of most intense headache; face continued flushed; pulse 140; temperature 104°. He continued vomiting freely; bowels constipated; urine high-colored. During the evening he began to cough up bile.

4*th.* Patient coughed up bile freely, and complained of a burning sensation in the right side. He always had to cough several times before the bile came up. The bile was of a dark-green color. Temperature 102°; pulse 100; pain less severe; headache less intense.

Patient continued in this condition until December 9th, when I saw him in consultation with Dr. Stark. He was then lying in bed with his head and shoulders raised. Pulse 108; respiration 22; temperature 102°; face flushed, skin slightly jaundiced. He coughed up bile at shorter intervals. During my visit he had two or three spells of coughing. He brought up at each time a large tablespoonful of bile. It never came without coughing. A half cupful was collected that day and sent to Prof. Hayes for analysis. He reported it to be pure bile, and used it as a specimen for testing in his physiological chemistry class. The urine was also found to contain a small quantity of biliary coloring matter.

On examination of the chest and abdomen I found that the depth of hepatic dulness on a line below the right nipple was six and a half inches. A friction-sound was heard over the upper surface of the liver in front. Coarse mucous râles were also heard over the anterior region of the right chest. On examination of the posterior region no abnormal sounds were heard; no dulness, no râles. So far as could be discovered, the physical signs existing were increased hepatic dulness, friction-sounds, and râles over the anterior and lower portion of the chest.

From this date the patient gradually improved. The amount of bile became every day less, and ceased rather suddenly on December 19th, ten days after my visit. His cough ceased at the same time. He went back to work on January 1, 1886.

During the attack the bowels were constipated, and when moved by a cathartic the passages were of a light grayish color. Patient remained well until April 13th. When riding in a street-car he commenced to cough, and on going out on the platform he felt a choking sensation and expectorated matter similar to that coughed up in the winter. This was not examined by the physician. He felt no pain, and after a few days' rest resumed his work. The cough and expectoration continued for two days and then ceased. During the attack he enjoyed fair health.

On *April* 21*st* the patient was carefully examined by Dr. Stark and myself. He is now quite free from cough and presents a very healthy appearance.

He is able to do an ordinary day's work. Pulse and temperature normal, and tongue clean; in fact, he seemed to be in excellent health. On examination of the chest we could find no abnormal condition. The area of hepatic dulness was normal, and there were no friction-sounds or râles.

After this period (April, 1887), for a period of over ten years, the patient enjoyed good health. He had attacks of alternating constipation and diarrhœa, and during the latter part he noticed that the stools were light colored. He also suffered almost constantly from an itching of the skin, which was not so severe as to prevent his sleeping.

In the early part of May, 1896, he noticed that his skin was becoming jaundiced, but did not consult a physician until the middle of the month. Late in the evening of Saturday, May 31st, he felt a severe pain in the right side in the region of the gall-bladder, which gradually became worse, and on the following morning he was seen by his physician.

Soon after the commencement of the pain he coughed a greenish fluid which was, no doubt, partly composed of bile. He remained in bed a month, and after getting up he noticed that his urine, which had previously been high colored, had now a dark-red tint. This passed away in two weeks' time. The attending physician thought that this change was due to the presence of blood, but neither a chemical nor a microscopical examination was made.

About the middle of July, 1896, the great toe of his right foot became swollen and very painful. The pain and swelling extended up the limb and became very severe. This lasted two weeks, and shortly afterward his left shoulder became swollen and painful, a condition which continued three or four days. He was not troubled with pain in any of his joints before, nor has he had an attack since.

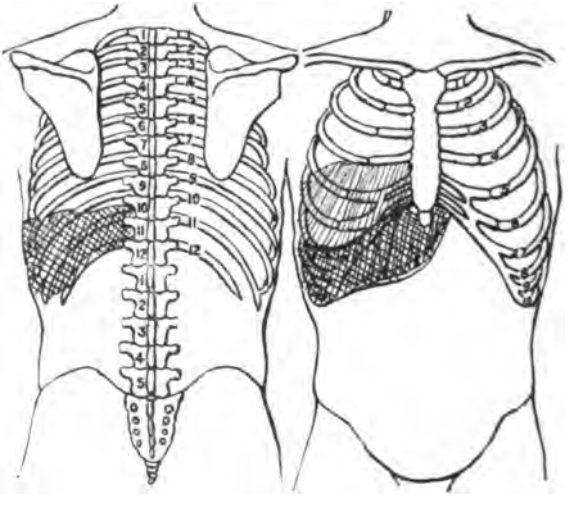
He continued to cough up bile from May 31st to November 22d, with the exception of two or three days, when he expectorated a large amount of mucus. The amount of bile varied from a few ounces to two pints. The skin during that time, although not normal in color, was not remarkably jaundiced. On the days when the biliary expectoration ceased he noticed a return of the jaundice both in the integument and in the conjunctiva.

Nov. 20, 1896. *Digestive System.* The tongue was somewhat swollen and covered with a yellowish-green film. His appetite was good, and he could eat ordinary food without inconvenience. Sometimes a disagreeable feeling of fulness in the stomach was noticed after dinner. The passages from the bowels during the summer were lightish in color, but in the last two weeks they became darker, and at this time were of a slightly greenish tinge.

On physical examination the abdomen was found slightly distended and tympanitic on percussion. The relative hepatic dulness in the nipple-line commenced at the lower border of the fourth rib, and absolute dulness at about the seventh. (See Fig. 1.) The lower margin of absolute dulness was found in the nipple-line at about two inches below the margin of the ribs. The lower line of dulness commenced on the left side at the seventh costal cartilage about an inch from the left border of the sternum, passing down-

ward to the right to a point at equal distance from the ensiform cartilage and the umbilicus, and a little to the right of the median line. It then passed horizontally to the junction of the cartilages of the ninth and tenth ribs of the right side. A distinct swelling was noticed below the costal margin which was more or less tender and felt somewhat elastic. The patient complained at times of pain in the gall-bladder region extending toward the umbilicus. The spleen was not enlarged.

FIG. 1.



The Respiratory System. The patient had spells of coughing which recurred at regular intervals, and were more distressing when he was in a recumbent position. The sputum contained bile and mucus. No pus was found. The chest was well developed and normal in shape. Expansion normal on both sides. The vocal fremitus was slightly increased on the right side. Dulness on percussion extended upward from one to two inches above the normal limit between the mid-axillary line and the sternum. From the mid-axillary line to the spine the lower margin of pulmonary resonance was in the normal situation.

Râles of various kinds, sibilant, sonorous, and coarse mucous, were heard in the right side below, from the mid-axillary line to the sternum. A friction-sound of a creaking character was also heard in front.

The impression given by physical examination was that the portion of the lung in front between the mid-axillary line and the sternum was probably the part through which the fistula passed.

Genito-urinary System. No pain or difficulty in passing water. Analysis

of urine: specific gravity 1020, reaction acid, albumin and sugar absent, bile-pigment present in small quantities; no casts.

Facial expression comfortable when not troubled with cough; but during an attack of the latter the face became livid and the lips cyanosed. Blood was examined microscopically and found normal.

His temperature was taken night and morning for a week, and was often subnormal and never higher than normal.

12*th*. The patient was examined by Drs. Tesky, Sweetman, and Stark, and the liver and gall-bladder were percussed. For some days after the examination the patient ceased coughing up bile, and the jaundice was not increased. At the same time the stools became more colored. The manipulation of the gall-bladder appeared to assist the passage of bile through the natural channels.

In *December* and *January* the patient again coughed up bile as he had done during the previous six months. The amount coughed up in twenty-four hours varied from a half to two pints. It was mixed with frothy mucus. Chemical examinations were made several times, when Gmelin's test showed the presence of bile. The general health of the patient had slowly declined during the summer, and in December he became much weaker.

At the consultation on November 12th an operation was advised to remove, if possible, the obstruction, so as to allow the bile to flow through the natural channels; and, if this were not possible, an opening between the gall-bladder and some part of the intestines was spoken of.

The patient decided to have an operation done, and on January 26th Dr. Sweetman, assisted by Drs. A. H. Wright and Stark, operated; I am indebted to Dr. Sweetman for the following note:

"The abdominal incision (six inches in length) was made in the right semilunar line.

"The muscles gave evidence of previous infiltration, and the fasciæ, when divided, passed rapidly out of sight, leaving a widely gaping wound. The peritoneum was deeply injected and the intestines distended and adherent.

"The fundus of the gall-bladder was packed around about and aspirated; six or seven ounces of dark-colored bile secured. The common and hepatic ducts could be felt distended with gallstones, the ducts measuring something over half an inch in diameter.

"As bile of fair color kept oozing up through the wound in the gall-bladder made by the aspirator needle, the obstruction in the hepatic and cystic ducts was thought to be but partial.

"As the gall-bladder was deep-set and separated by several inches from the abdominal wall, and the patient was coughing more or less constantly, it was not thought possible to bring about adhesion of the gall-bladder to the abdominal wall. Owing to the distended and adherent condition of the intestines, and the known tendency of the patient to bleed, it was decided not to disturb the adhesions and incise the cystic and hepatic ducts, especially as this would involve leaving the abdominal wound partially open for drainage,

with the risk of having a loop or loops of intestine forced out by the violent and prolonged coughing. The wisest course under the circumstances seemed to be to do a cholecystenterostomy, which was done, making use of the hepatic flexure of the colon instead of the duodenum, with the hope that the gallstones, which appeared to be small in size, would gradually find their way into the gall-bladder and on through the newly formed opening into the bowel.

"The patient died on the twelfth day from hemorrhage from the nasal mucous membrane, the stomach, and gall-bladder."

Patient did fairly well until about the sixth day after the operation. During the first three or four days he continued to cough up large quantities of bile, but after that the amount was not so great. The cough was very distressing, so much so that on third day, during one attack, the sutures were torn through the abdominal walls and had to be replaced.

On the sixth day the patient coughed up matter having a disagreeable odor, which suggested the possibility of bowel contents; but the sputum was examined for the bacillus coli communis and it was not found.

The temperature gradually rose, and evidences of pneumonic consolidation developed in the anterior and lower part of the right lung. On the eighth day he coughed up some blood, afterward the cough became more constant and the hæmoptysis more marked. The sputum at times was largely made up of blood and bile; on the ninth day the amount of blood was increased; on the tenth coagula appeared in the sputum. On the same day the patient had a severe attack of epistaxis; this continued for some hours, and plugging of the nostrils became necessary. On the eleventh day the cough and hemorrhage ceased, but returned to a slight extent on the twelfth day. Death took place on the twelfth day after the operation. During the last few days of his life blood passed in large quantities from the bowels, and during the last week patient became intensely jaundiced.

The temperature did not rise above a hundred except on one occasion, when it reached 101° F.

In the latter part of the illness the blood became more fluid. I regret very much that it was quite impossible to obtain a post-mortem examination.

In my opinion we may safely conclude that in the former illness, which occurred ten years ago, the obstruction to the flow of bile was of a temporary character, and on its removal the sinus to the bronchus closed up. It would appear, however, that this closure, although it lasted ten years, was easily overcome, because in the last illness the patient expectorated bile very shortly after the symptoms of acute biliary obstruction made their appearance. In the latter attack the obstruction was of a more permanent character—calculi lodged in the common bile-duct. It was not, however, complete at all times, as shown by the coloration of the stools.

Death was due to several causes. The constant coughing disturbed

the parts operated on, and the hemorrhage probably took place from a congestion of the gall-bladder mucosa. At the same time the sinus through the lung became closed either by blood-clot or pneumonia, so that only a small amount of bile was expectorated. The patient then became intensely jaundiced, a condition which accounted for the general hemorrhage which supervened.

There were no special signs of any terminal infection except the pneumonia. In such rare cases one cannot foresee the results of surgical interference, but this case showed that it was necessary to make at once a free opening for the bile to pass in some safe direction so the patient might have rest from coughing.

Then in making an opening between the gall-bladder and any part of the intestinal tract the possibility of a regurgitation of the contents of the canal into the biliary passages and then into the lung ought to be considered. (Under the head of fistula between the biliary passages and pleura or lung, Courvoisier mentions the fact that such fistulas are rare, and usually result from tropical abscesses of the liver.)

Besides those produced in this way, Courvoisier tabulated twenty-four cases. I have collected eight, which occurred since the publication of Courvoisier's work. These, with the one now given and one of Barth's, make ten cases, or thirty-four altogether. Of Courvoisier's twenty-one cases six were described during life, and the diagnosis in each was confirmed by the presence of bile in the expectoration. Recovery took place in all. In two of the six cases no cause was discovered; the origin in one was thought to be calculous obstruction in the hepatic duct. In one case hydatids without abscess, and in the remaining hydatids with suppuration were present.

In the eighteen fatal cases post-mortem examinations were made; echinococci were found in six, and in two cases ascarides were the cause of the perforation.

Ten were cases of cholelithiasis, and in four of them the right lung was grown to the diaphragm, and the fistula was found within the adhesion. In the latter ones there was no pleural effusion. Since they more nearly resemble the one just described, I will give briefly the pathological conditions found in three of the cases:

1. Bristow's case.(*a*) Patient, a female, aged thirty-two years, suffered from intense jaundice and other symptoms of hepatic disease. A few days before her death she commenced to cough up bile. At the post-mortem examina-

tion the lower part of the right lung was found adherent to the diaphragm. It had a leathery, tough consistence, and was slate-colored. A fistula was found passing through the diaphragm communicating with the bronchial tube.

The common bile-duct was obstructed by a calculus. Dilatation, suppuration, and destruction of the hepatic ducts were observed. Cavities existed in the liver, some as large as hen's eggs. One of the latter, the largest, was situated at the convex surface of the right lobe and communicated with the lung. The contents of this, as well as of the other cavities, were soft, pulpy, and of an olive-green color. The diaphragm was firmly adherent in the liver and lung, and presented an opening which corresponded to the opening situation of the abscess.

2. Dreschfield's case,(*b*) described in my former paper, and which more closely resembled the one now under consideration than any one of the tabulated cases.

3. Gaston's case, Atlanta, Georgia.(*c*) The patient, a middle-aged man, suffered from symptoms of biliary obstruction, and a few days before death began to cough up offensive bile much stained.

At the post-mortem the common bile-duct was found to be completely occluded.

"A collection of disorganized bile and serous exudation which was, doubtless, confined in the dilated sac of the gall-bladder, had made its way into a cavity found between the upper surface of the liver and the lower surface of the diaphragm, and extended through an aperture into the pulmonary bronchi. The flow of the offensive matter into the bronchial tubes seemed to be the immediate cause of death."

4. Laboulbene's case.(*d*) Male, aged forty-one years. Enlargement of the liver; broncho-biliary fistula; spontaneous cure. October 4, 1875. The patient when in good health went on a journey, and while away was seized with a violent cough and expectorated a greenish fluid which had an offensive odor and contained pure bile. This continued until the following March, when he was admitted into the hospital. He improved under treatment, and in May was discharged quite well. Mucous râles were heard over the right lung.

The following five cases of broncho-biliary fistula have occurred since the publishing of Courvoisier's book.

1. Carter's case.(*e*) A woman, seventy years of age, had good health, with the exception of occasional severe spasms in the hepatic region. Four years before the notes were taken she had suffered from biliary colic, followed by jaundice. These attacks recurred every five or six months until July, 1888, when, after a severe paroxysm of pain, jaundice supervened and became persistent. A month after this the patient had what seemed to be bronchitis, during which she coughed up large quantities of bile. Moist râles were heard in the lower half of the right lung, but there was no tenderness in the right

hypochondriac. The expectoration of bile continued with occasional intervals until April, 1889, when the patient gradually sank, and died. A post-mortem examination was not made.

2. Adam's case(*f*) is of special interest in this connection. The patient, aged seventy years, had had for six or seven previous years severe attacks of jaundice, lasting a week and then passing away.

In January, 1889, jaundice appeared, accompanied by moderately severe pains in the hepatic region. These symptoms persisted until July of the same year, when severe pain was experienced in the region of the liver. Two days afterward the pain ceased, when she coughed up bile. Patient could not lie down on account of the severity of the cough. Signs of acute bronchitis were present in the right lung. Temperature normal. No change in right hypochondrium. Patient continued to expectorate bile during the next four days, when the jaundice partially disappeared. Consolidation of the right lower lobe then took place, and the expectoration of bile ceased. The patient became intensely jaundiced, and the distended gall-bladder could be felt below the liver. Death from cholæmia and marasmus. No post-mortem examination. In this case the immediate cause of death appeared to have been the complete closure of the broncho-biliary fistula by the pneumonia and the subsequent cholæmia.

3. Colvee.(*g*) A general in the army who had been some years in the tropics and had suffered from hepatic disease, the result of malaria. For four years he had attacks of bronchitis, and on October 7, 1889, he was seized with a severe pain in the hypochondrium, accompanied by fever and vomiting. After some days he commenced to cough up bile. This continued until May, 1890, when the notes were written. The patient on several occasions coughed up small biliary calculi, which fell into the spittoon with a distinct noise. They were not examined chemically.

The author concluded that the patient suffered from hepatic calculi, which has been the centre of an abscess that perforated the diaphragm into the lung.

4. G. C. Macdonald's case.(*h*) The patient, a male, aged forty-nine years, commenced to cough up bile in the latter part of March, and this continued until June, when it gradually ceased. On June 15th the patient coughed up three small gallstones, two of which were facetted, about the size of a split pea. The other, half an inch long and one-eighth of an inch in diameter, formed the mould of a tube. The patient ceased expectorating bile and rapidly recovered his health. He had syphilis, and potas. iodide was given at the same time.

5. Visserung's case.(*i*) The patient, a male, aged three years, suffered from pain in the right side in the cæcal region. The seat of pain moved afterward to the under surface of the liver. Signs of pleurisy were discovered, and shortly afterward the patient began to cough up foul-smelling pus and bile. Jaundice, which had previously existed, now disappeared. About two months subsequently to the commencement of the bilious expectoration

the patient coughed up a gallstone the size of a bean, of a brownish color and with a roughened surface. After this the biliary expectoration ceased and the patient recovered gradually. When the report was made the patient could take outdoor exercise.

6. Cattani's case. A female, aged forty-eight years. Previously in good health. Suffered at first from pains in the hepatic region and from digestive disturbances. She afterward coughed up bile and pus. Sometimes lung and liver tissue and striated membranous fibre were found in the expectoration. Patient suffered from jaundice, and a tumor was noticed in the hepatic region. An inflammatory process followed by suppuration began in the liver and extended through the diaphragm into the lung. Cattani gives a most exhaustive account of the case. Patient recovered. The probable cause was calculi in the common duct.

The cases which I have collected, in addition to those of Courvoisier, are ten in number, including the one now reported. All of these were published since 1889 except Barth's.(*j*) Of these, two were due to hydatids, and the remaining eight to biliary calculi.

The diagnosis of broncho-biliary fistula is not difficult. There are cases of pneumonia and bronchitis occurring in connection with jaundice when the expectoration is stained with bile. When a fistula is present the amount and purity of the bile are sufficient to render the diagnosis certain. The bile is sometimes expectorated in very large quantities, as high as 700 c.cm. per day.

The physical signs have been very uniform in the cases described. Dulness in some extended as far back as the mid-axillary line and forward and inward to the margin of the sternum and upward as far as the third intercostal space. In one case, Laboulbene's, dulness was marked over the posterior part of the right lung. Roughened breathing, somewhat bronchial, was heard over the same area, and, in some instances, loud mucous râles were also heard.

The cough is usually a very distressing symptom, and in many cases the patients were not able to lie down on this account. It is probable that so long as the bile is passing through the right lung in large quantities it may, when the patient is in a recumbent position, find its way into the left lung, thus interfering with respiration.

According to the pathological reports, broncho-biliary fistula in cholelithiasis may begin in three or four different ways. The occlusion of the common bile-duct by a calculus may be followed by a suppurative cholangitis and the formation of abscesses in the liver. A

large one near the convex surface may extend upward through the capsule and diaphragm into the lung. Adhesive inflammation preceding the extension of the abscess would prevent the entrance of pus into the pleural cavity.

2. After the close of the ductus communis choledochus intra-hepatic calculi may form and become the centre of an abscess, which, if it exists near the convex surface of the liver, may find its way into the lung in the way already described.

3. One or more gallstones from the gall-bladder or larger bile-ducts may perforate the liver and diaphragm into the lung. The writer not long ago was present at a post-mortem examination of a gallstone case, in which an abscess about the size of an orange was found in the right lobe of the liver. The cavity, which nearly perforated the convex surface, was continuous with that of the gall-bladder. It contained a large number of calculi. In such a case one can easily understand that by a continuation of the process a broncho-biliary fistula would be established.

4. It is quite possible that a gall-bladder in a state of inflammation may rupture and a circumscribed abscess result which may be situated on the upper surface of the liver between it and the diaphragm, and that the abscess may perforate the diaphragm into the lung or pleural cavity.

Laboulbene mentions the possibility of bile passing directly from the gall-bladder into the bronchi, and quotes two cases in which a communication was found between the gall-bladder and an abscess-cavity on the convex surface of the liver.[1]

Courvoisier mentions four cases in which this direct commmunication existed. In one of these the abscess ruptured into the mediastinum and then into the right bronchus, and in another it perforated directly into the lung. In the other two empyema was also present.

The aseptic non-irritating character of the bile is well exemplified in these cases. In some cases the fistula lasted several months without exerting any injurious effects on the lung, and in those in which pneumonia supervened there was evidence of septic infection.

When the fistula is once formed the passage of the bile upward is not so difficult as might be imagined. The pressure of the diaphragm

[1] Bercroix: Bull. de la Société Anatomique, 2d série, 1857, 2 p. 178.

downward in respiration favors the flow of bile into the bronchus, and coughing assists it further.

The second case which I wish to present to the Association is one perhaps of greater interest to the surgeon than the physician, since the broncho-biliary fistula was formed after an injury. The patient, a man, aged twenty-five years, had enjoyed excellent health up to the time of the accident. There was no history of biliary colic, no syphilis, and no tuberculosis.

The patient was kicked by a horse January 28, 1897. The blow was received over the cartilages of the fifth, sixth, seventh, and eighth ribs. He was standing at the time, and was not knocked down. The contusion was not marked nor even the cartilages injured. He felt immediately a severe pain beneath the part struck, as well as in the right shoulder. He was able to walk to the house, and since his sufferings rather increased than diminished, Dr. Thomson, of Galt, was sent for. The physician arrived about four hours after the accident, and found the patient suffering from most severe pain of a spasmodic character, both in the hepatic region and in the shoulder. The stomach was very much distended, and he had frequent eructations of gas which seemed to relieve the pain. He at the same time expectorated mucus tinged with blood. A hypodermic of morphia was given which relieved the pain. It was necessary to continue the morphia for four days after the accident. At that time pneumonia developed in the lower and anterior part of the right lung. After about a week's time inflammation of the lung subsided, but the consolidation did not altogether disappear. Fluid then formed in the right pleural cavity.

The patient began to cough up bile about February 15th. The quantity was small at first and came up after a severe attack of coughing. Afterward it came up in larger quantities and with less effort. The amount of bile and mucus expectorated in twenty-four hours was never more than a pint, and, as a rule, much less. On February 23d the right pleural cavity was aspirated and about a pint and a half of bile stained with serum and pus was drawn off. On the following day an opening was made and a drainage-tube introduced. For some time the bile-stained fluid made its way through the tube, but after a week or so the green color disappeared. So that now (April 8th) a small quantity of serous purulent fluid escapes from the opening.

The expectoration of bile increased after the operation. Jaundice was not present at any time. After the operation the temperature fell to normal, and remained but slightly raised for a week, when it again began to ascend. At the same time an increased area of dulness was observed in the hepatic region, and on aspiration about a pint of bile and mucus was drawn off.

On March 2d a second operation was determined on, and an incision was made from the mid-axillary to the anterior axillary line, and portions of the

sixth and seventh ribs were removed. A second drainage-tube was introduced directly below the first, through which mucus and bile flowed.

After the second operation, the color of which had been normal, bile disappeared from the stools.

The patient was seen by the writer on April 8th, when the following conditions were found: he was pale and somewhat emaciated, and could sit up with difficulty. He did not complain of much pain when quiet. The posterior portion of the right chest did not present any abnormal condition except that the pulmonary resonance extended only to the ninth interspace. On the anterior surface resonance was normal as far down as the fourth rib, and then absolute dulness was observed down to the sixth rib. Below the sixth rib to the costal margin a tympanitic note was present. The resonance on the right side was noticed over an area very similar to that of the semilunar space on the left side. (See Fig. 2)

FIG. 2.

On the right side the line of incision from the fourth rib to the eighth was plainly seen. Two openings were present in which were drainage-tubes. The upper opening through the sixth intercostal space in the anterior axillary line gave vent to a small quantity of pus. The lower opening through the seventh intercostal space near the mid-axillary line gave exit to a green-colored fluid composed of bile and mucus. When the drainage-tubes were removed and the patient coughed the quantity flowing through both openings increased, and bubbles of air or gas produced a foam at both openings. The amount of gas which passed through the lower opening was much greater than that through the upper.

The openings did not communicate readily with one another, since fluid injected into one never passed out through the other. At different times during the progress of the case the bile flowed in the different channels: 1, through the bronchi; 2, through the pleural cavity and out of the upper

opening; 3, into a cavity on the convex surface of the liver and through the lower opening; 4, through the common bile-duct.

When I saw the patient on April 18th the bile passed upward through the lungs and outward through the lower opening.

After the second operation Dr. Thomson remarked that the patient suffered from severe pain in the right shoulder when the finger was introduced into the lower opening.

He also noticed that the bile flowed in larger quantities after ¼ grain of calomel had been given every hour for five or six doses.

The history points to a partial closure of the common bile-duct and to the existence of a cavity beneath the diaphragm, which was either a distended gall-bladder or an abscess with which the gall-bladder communicated freely.

Direct communication also existed between the biliary passages and the pleura and bronchi.

Before the second opening was made the obstruction in the common duct was apparently not so complete but that it was not overcome, and the bile passed into the duodenum. Afterward the exit through the chest-wall was easier and the bile ceased flowing through the natural channels.

It is difficult to make an accurate diagnosis in such a case as this. There is no doubt a displacement of the liver backward so that the anterior border with the wall of the gall-bladder was brought into close contact with the diaphragm.

A rupture of the diaphragm had taken place at the time of the accident. I would have expected greater collapse. This would account for the very severe pain, and possibly for the pulmonary hemorrhage, but the latter might be due to contusion.

Cases of laceration of the liver have been described which were followed by little hemorrhage, although the opposite is the general rule. Lacerations of the liver have been known to occur from very slight injuries. A blow which is not heavy enough to produce much contusion of the skin may cause laceration of the liver. One case is mentioned where a quick turn in bed when the patient was very much frightened, was the only cause which could be discovered for a laceration in the posterior part of the right lobe of the liver.

Dr. Peter (*Gaz. des Hôpitaux*, 1890, p. 726) reports a case in which a blow over the liver resulted in perihepatitis and pleurisy on the right side. Dr. Peter thought there had been a wound of the liver substance. There was no interference with the biliary functions.

Dr. Thomson and Wardlaw, of Galt, to whom I am indebted for the history of this case, have recently (April 26th) reported that the

patient is slowly recovering. The bile passes largely into the bowel, and the stools have become normal in color. The patient coughs up very little bilious fluid, and very little finds its way through the lower opening.

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A CASE OF ACROMEGALY: AUTOPSY: SKELETON.

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This case was first reported by me in *The American Journal of the Medical Sciences* for June, 1892, and since that date has been more or less constantly under my supervision.

Three years ago he had several bad attacks of epistaxis and a great deal of muscular prostration; he then for a time regained his muscular power, and was able to resume his work as a machinist, working pretty constantly during the last two years. Ever since he has been under my observation he has had short periods of passing diminished quantities of urine, and has complained of some lumbar pain. He has never been free from a constant, almost unceasing, tinnitus aurium. He has had occasional attacks of dizziness during his last years, but there have never been any signs of mental aberration other than the temporary derangement lasting one month, in 1887, as reported by me in my first article. The last few years he has not had as much headache as in previous years.

Since the report in 1892 he has increased a great deal in size and weight.

In May, 1896, he went to the New Haven Hospital, where he remained for five days only, complaining of pain in the right ear and ringing in both ears. On May 20th a trace of albumin was found in the urine, also a trace of sugar and some granular casts. On May 24th the records show no albumin and no sugar.

During the last six months this patient has been occasionally to my office for minor conditions, such as constipation, a slight cold, etc., but on December 1, 1896, he sent for me, showing considerable œdema of the feet, legs, and scrotum, but none of the upper part of the body. Examination of the heart, as taken from my records, showed no lesion, although the sounds were rather muffled and indistinct. The pulse was good, but slow, registering 65. The amount of urine passed was scanty, but on repeated examinations during the next three weeks showed no casts and no albumin until the day before death, when ½ per cent. of albumin was found, but no casts and no sugar. He did not show any signs of uræmia. A few days before his death the œdema of the feet and legs became very much increased, and there was also

a considerable amount of ascitic fluid in the abdomen, and some slight œdema of the lungs. The patient died on December 28, 1896, suddenly and unexpectedly, with signs of simple syncope; in other words, he died in the manner described by Marie in his early description of this disease. There was no previous history whatever of cardiac distress or angina.

He was forty-seven years old at the time of his death, and had had his disease for twenty-three years, the first symptoms having appeared at the age of twenty-four years.

The *post-mortem* was made thirty hours after death, and showed that he died of acromegaly and not from any single complication or concurrent disease.

His estimated weight was at least 300 pounds, and the measurements of the body are much greater than those recorded in 1892.

At the level of the ensiform cartilage the body is fifty-three inches in circumference (forty-five inches in 1892). The circumference of the chest at the nipple line is fifty-one and one-half inches (forty-five and one-half inches in 1892). The circumference of the neck is twenty-one inches. The circumference of the cranium around the occiput and superciliary ridges is twenty-six inches (twenty-four inches in 1892).

Rigor mortis was about normal. The scalp was thick and covered with an abundant growth of coarse hair. The abdomen was greatly distended, and the lower extremities, scrotum, and penis were very œdematous. The blood in the legs was in the arteries and not in the veins, probably on account of the œdema so pressing upon the veins as to prevent the elasticity of the arteries sending the blood into the veins after death. The fat of the abdominal walls was considerable in amount, and largely injected with blood, the vessels being dilated. There was a large amount of ascitic fluid in the abdominal cavity.

On cutting through the ribs the medulla of the bones squeezed out, being soft, and of a reddish color. In the right pleural cavity was a large amount of dark-colored serum, and the left pleural cavity contained a small amount of yellowish serum, as did the pericardium.

The heart was enormous, being fifteen inches in circumference at the base of the ventricles, and weighed two pounds and nine ounces. From the auriculo-ventricular junction over the left ventricle to its apex is seven and one-half inches, while the length of the inter-ventricular septum is eight and three-quarters inches. The right side of the heart, both auricle and ventricle, was filled with blood. The wall of the right ventricle was three-eighths of an inch thick, and the wall of the left ventricle was seven-eighths of an inch thick. The valves of the heart were normal except some slight thickening at the edges of the aortic valves, with a small calcification half an inch from the valve on the aortic wall; otherwise the aorta is not diseased. The coronary artery is enlarged, admitting an ordinary lead pencil into the orifice. No occlusion of the heart-vessels was found.

The left lung weighed two pounds and fifteen ounces, and was normal

throughout, except that it showed a slight amount of œdema. The right lung showed a small patch of firm adhesions at its apex posteriorly, which, however, were easily broken down. There was some fibrous cicatrices and calcareous deposits at the apex of this lung.

The intestines were normal, except all through the abdomen were found a good many irregular peritoneal adhesions (the clinical history showed irregular abdominal pain). The large intestine was adherent to the spleen and to the base of the liver.

The stomach was dilated, and the walls were thinner than normal, with no signs of acute or chronic congestion. The spleen was enlarged and lobulated, and weighed two pounds and four ounces. The capsule was not adherent, but was thickened. The splenic substance was quite hard in consistency, and cut with a smooth surface, the cut surfaces being quite dark; there was considerable connective-tissue hypertrophy throughout.

The liver was enormously enlarged, weighing seven pounds and two ounces. The liver felt hard, and the capsule was slightly thickened; the cut surface was light in color, with a slight nutmeg appearance.

The gall-bladder was dilated and hung below the liver lobes, and was filled with gallstones. The suprarenal capsules were enlarged.

The right kidney contained three large cysts which were evident before the capsule was removed; one of these cysts would hold a small egg. The cortical substance was thinner than normal. The weight of the right kidney was eleven ounces after the cystic fluid was removed. The left kidney weighed ten and one-half ounces and presented no cysts on the external surface, but one small cyst was found on opening it.

The thyroid gland was enlarged and weighed 101 grammes. A large gland, weighing 36½ grammes, which proved to be an extra thyroid, was found in the median line high up in the chest-cavity, just above the upper end of the sternum. The left median nerve was enlarged and showed a marked swelling for one inch of its extent.

Cranium. The cartilages of both external ears in several places had become bone. The bones of the cranium were much softer than normal, while the spongy tissue was increased in thickness and very vascular. The thickest part of the cranium was found at the right side of the head in the occipital bone.

There was a calcification in the dura mater directly over the longitudinal sinus about on a line with the external ears, the greatest amount of this calcification being at the right of the longitudinal sinus. The brain was not injected more than normal, and without the dura mater weighed three pounds.

The convolutions of the brain were normal.

The right vertebral artery showed a cylindrical enlargement for three-eighths of an inch, beginning one and one-quarter inches from its junction with the opposite vertebral artery. The coats of the artery at this part were thickened and hard. The whole right vertebral artery was distinctly larger than the left, while the left vertebral artery was quite small for an inch before

its junction with the right vertebral. Also there was a distinct narrowing of the left artery about an inch before its junction with the right basilar artery, and it was distinctly misplaced from the median line toward the left, with its convexity toward the left. The two posterior cerebral arteries were of the same size, while the posterior communicating arteries, if present, were very small. The other parts of the circle of Willis were normal. The cranial nerves all appeared normal. A small tumor, about the size of a pea, was attached by a few fine fibres in front of the right crus cerebri at its upper part, behind the right optic tract, and lateral to the right corpus albicans.

On the right hemisphere of the cerebrum, at the upper end of the precentral sulcus, and extending more in front of this than behind, alongside the longitudinal fissure, is a roughened spot, three-fourths to seven-eighths of an inch in diameter, corresponding to the calcified area in the dura mater. A similar spot, somewhat smaller, was in a corresponding position on the left hemisphere. A needle thrust through the corpus callosum to the base of the brain, between the centres of these areas, comes out in the position of the pituitary body.

The superior and inferior longitudinal sinuses were normal, but the tentorium cerebelli was ossified at its attachments.

The velum interpositum and choroid plexus were thinner than normal.

Careful examination showed nothing abnormal in the substance of the cerebrum or cerebellum.

Sella turcica and its boundaries. In the sella turcica, which was very much enlarged, was a pulpy mass, containing a cyst, which was ruptured in removing the brain. This cyst contained yellow serum under considerable tension.

The cavernous sinuses and internal carotids were all pressed upon by the pituitary cyst, most marked on the right side. There were several little tumors attached to the inner surface of the dura mater covering the dorsum sellæ. There were also several small tumor-growths on membrane covering the pituitary body. There were more fibrous bands than usual in the cavernous sinuses, especially on the right side, so that the canal was much contracted. This was true on both sides, but most decidedly on the right.

The cyst-cavity in the sella turcica was S-shaped, enlarged at both ends, dipping down nearly to the bottom of the sella turcica, and bending around the right internal carotid forward and lying between the internal carotid on the inside and the cavernous sinus on the outer side. The right Gasserian ganglion seemed pushed a little outward and forward.

I am indebted to Dr. C. J. Bartlett, Assistant Professor of Pathology at Yale, for the following report of the examination of the specimens taken at the autopsy:

THE PATHOLOGICAL FINDINGS BY DR. C. J. BARTLETT. All of the tissues received for microscopic examination were either put at once into Zenker's fluid, or into Müller's fluid for a day or two and then into Zenker's. This consists of Müller's fluid saturated with corrosive sublimate, to each 100 c.c. of which 5 c.c. of glacial acetic acid is added when used. After being

in this for twenty-four hours and then washed in running water for twenty-four hours, they were hardened in alcohol and imbedded by the celloidin process. The corrosive sublimate is removed by treating the sections before staining with Gram's iodine-potassium iodide solution for fifteen minutes, and then rinsing in alcohol.

The chief pathological changes are seen in the contents of the sella turcica and adjacent tissues, in the thyroid body, and in the presence of a thoracic thyroid gland.

Sections of the soft material taken from the *sella turcica* (Plate I., Fig. 1) consist chiefly of cells showing no regularity of arrangement, and with almost no fibrous tissue between them, but having a small amount of granular intercellular material. The cells are not in contact with each other, as a rule, but between them spaces are left, these intercellular spaces occupying a larger part of the field in some portions of the section than the cells do. Thin-walled bloodvessels are numerous, although blood-corpuscles are not present in the smaller vessels, nor between the cells of the tissue. In places the bloodvessels are in contact with the cells, in others they run through open spaces with apparently no other support than that of the endothelial cells forming their walls. The cells of the section vary greatly in size and appearance. In shape the greater number are either round or oval. The smallest consist simply of a single deeply staining, round nucleus, five or six microns in diameter, surrounded by a thin border of granular protoplasm. At the other extreme in size are cells twenty microns or more in diameter, containing from four to ten small, deeply staining, round or oval nuclei, the nuclei in some being collected at one side of the cell or arranged around the periphery, in others being scattered throughout the cell-protoplasm. A majority of the cells are intermediate in size, containing from two to six nuclei and having a granular protoplasm.

A section through the Gasserian ganglion and cavernous sinus of the right side (Plate I., Figs. 2 and 3) shows masses of cells, quite similar to those described above, between the bundles of nerve-fibres of the fifth nerve, while the wall of the cavernous sinus is largely replaced by this cellular growth, which is evidently an invasion of the adjacent tissues by the growth in the sella turcica. The nuclei of the cells are many of them slightly larger than in the section above described, and are more vesicular, not staining as deeply. A few of the cells consist almost wholly of a collection of these vesicular nuclei, four or more in number, massed together with little cell-protoplasm between or around them. The thin-walled bloodvessels are filled with blood, and in places the red blood-corpuscles lie between the tissue-cells.

Sections through the left Gasserian ganglion show a smaller number of similar cells, the new growth not having invaded the surrounding tissues as widely here as on the right side. In sections of both the right and left Gasserian ganglia the nerve-tissue appears normal.

The small tumor-growth which was attached to the right crus cerebri (Plate I., Fig. 4), as well as those from the dorsum sellæ, show a similar structure

PLATE I.

FIG. 1.

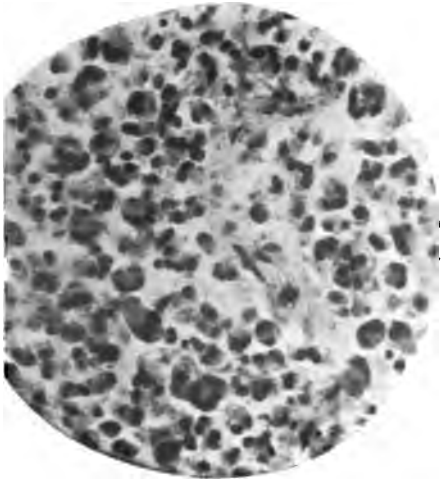


FIG. 2.

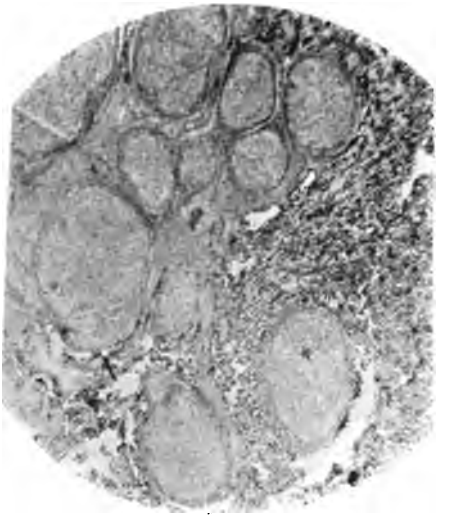


FIG. 3.

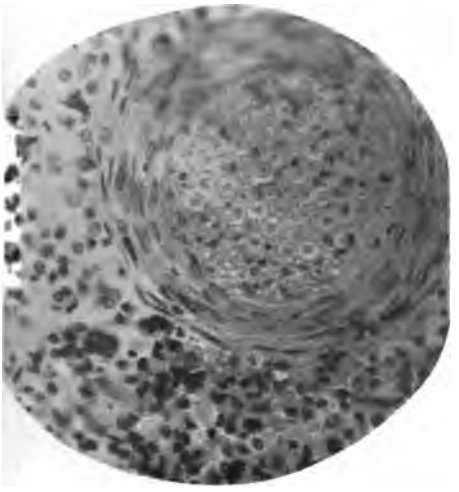
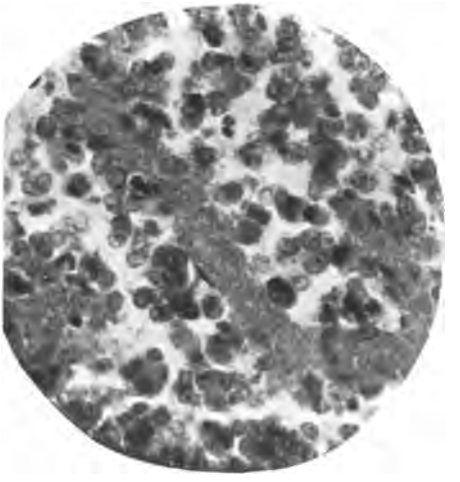


FIG. 4.



OSBORNE'S CASE OF ACROMEGALY.

FIG. 1.—Pituitary body: ¼ in. obj. FIG. 2.—Fifth nerve, tumor cells; 16 m.m. obj.
FIG. 3.—Gasserian ganglion, fifth nerve; ¼ in. obj. FIG. 4.—Tumor of right crus cerebri; ¼ in. obj.

to that described, the vesicular nuclei and the massing of several of these in a single cell surrounded by only a small amount of protoplasm being even more noticeable than in the sections of the Gasserian ganglia. In places there is considerable hemorrhage into the tissue.

The source and classification of the growth filling the sella turcica, and invading the surrounding tissues, with the small secondary tumors described, are somewhat doubtful. No regular grouping of the cells is noticeable aside from a slight columnar arrangement in places in the small tumors, the centres of some of the columns of cells being occupied by a small bloodvessel; and probably it is to be classed among the sarcomata, but whether endotheliomatous in origin, or not, could not be determined. The gross appearance of the small nodular growths on the dorsum sellæ was similar to that seen in disseminated endotheliomatous nodules of the peritoneum, and produced a prejudice in favor of such a diagnosis, but this could not be confirmed microscopically.

In the *thyroid gland* (Plate II., Fig. 5) the most noticeable change from normal is a marked increase in the connective tissue, there being comparatively thick bundles of this between the vesicles. The larger vesicular spaces contain colloid material, while the smaller are filled with groups of epithelial cells.

The *gland* found in the upper part of the thoracic cavity (Plate II., Fig. 6) shows a distinct division into cortical and medullary portions, the latter constituting somewhat more than half the diameter of the entire body, and being made up of fibrous tissue. The cortical portion resembles that of developing thyroid tissues as described by Halsted as being found in dogs after partial extirpation of the thyroid gland.[1] This gland is surrounded by a fibrous capsule, richly supplied with bloodvessels, and bundles of fibrous tissue extend from this into the cortical portion. This cortical portion is composed of vesicular spaces, varying in size from those 2 mm. long to those of microscopic dimensions, between which are thin bundles of fibrous tissue with numerous small bloodvessels. The spaces are lined with cells, cuboidal or slightly columnar in shape, each cell containing a single deeply staining nucleus. The cells may be one layer deep, or there may be several layers, and many of the smaller spaces are completely filled with cells. The larger spaces are oval in shape, elongated perpendicularly to the surface of the gland, and most of them contain more or less homogeneous colloid material, some of them being only partly filled with it. Others are filled with cells, or partly with colloid material and partly with degenerating cells, the outlines of which may still be made out.

Of the *nerve-tissues*, sections were made and examined by Dr. Robert E. Peck, from both Gasserian ganglia, from different portions of the medulla, and the upper end of the spinal cord, from the pons, the right crus cerebri, the left crus cerebelli, the median nerve of the left side, and from the pos-

[1] Halsted: "Experimental Study of the Thyroid Gland." Johns Hopkins Hospital Reports, vol. i.

terior tibial nerve of the right side. These all showed normal structure except the lower end of the medulla, the median nerve, and a small branch of the posterior tibial nerve.

A cross-section of the lower end of the medulla showed, to the naked eye, an atrophy of the posterior column of the left side for the extent of 5 mm. Microscopically there was seen to be a disappearance of nerve-fibres in this portion, and an increase of fibrous tissue, this increase not being sufficient to replace the nerve-tissue that had degenerated, leaving the left posterior column smaller than the right. The left median nerve had undergone such post-mortem changes before hardening that a minute microscopic examination was impossible. The whole section, however, showed a great increase in fibrous tissue between the bundles of the nerve-fibres.

A small branch of the posterior tibial nerve showed sclerosis. The pineal gland did not show any pathological changes.

Sections through the *heart-wall* (left ventricle) show a marked increase in thickness of both the pericardium and endocardium, and an increase in fibrous connective tissue between the muscle fibres, most marked near the endocardium. In some of these fibrous bands are collections of fat-globules. The heart muscle-fibres, many of which are large, have pronounced longitudinal striations. The intima of the small bloodvessels in the wall of the heart is thickened.

The condition of the *lungs* is that resulting from the inhalation of excessive amounts of some kind of dust accompanied by chronic passive congestion and slight emphysema. The most noticeable changes from normal are the masses of pigment and the thick bundles and irregular-shaped masses of connective tissue present. The pigment is found in the lymphatic spaces around the bloodvessels, and around the small bronchioles, and is irregularly distributed throughout the thick bundles of connective tissue. These connective-tissue masses contain thin-walled bloodvessels, and around the periphery of many of the masses are collections of lymphoid cells. In other places the alveolar walls are thickened; there has been a proliferation and desquamation of the epithelial cells lining these, so that the air-cells are more or less filled with them, and many contain pigment-granules, while in still other fields the alveolar walls have become thinned and broken, leaving emphysematous spaces. There were no tubercles found in the lungs.

The *liver* shows beginning cirrhosis, and in places slight chronic congestion.

Sections of the *kidney* show the organ to have been congested. There is an increase in connective tissue below the capsule and a slight increase between the uriniferous tubules in places, and the walls of a few of the glomeruli are thicker than normal. The intima of the small bloodvessels is thickened. In the tubules there is some granular detritus, but this condition is not marked, nor is the granular appearance of the protoplasm of the cells lining the tubules marked. One of the uriniferous tubules noticed in the pyramidal portion was distended, and contained a collection of red blood-

PLATE II.

FIG. 5.

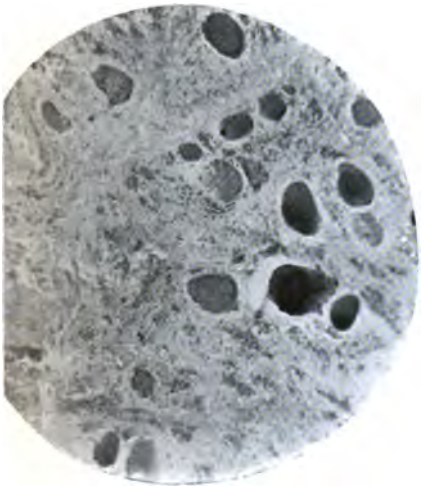


FIG. 6.

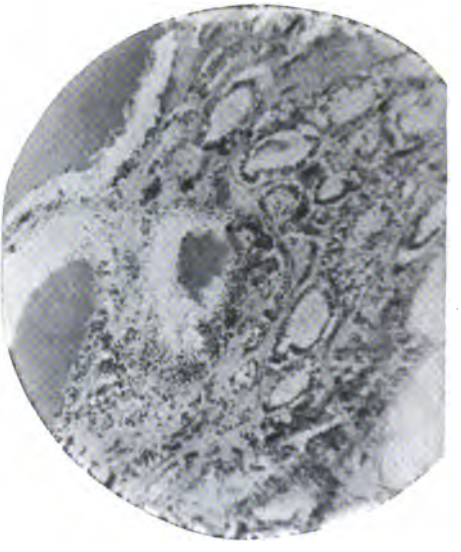
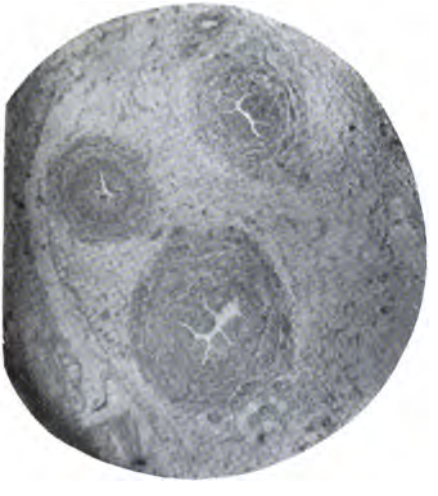


FIG. 7.



OSBORNE'S CASE OF ACROMEGALY.

FIG. 5.—Thyroid gland.
FIG. 6.—Thoracic Thyroid ; 16 m.m. obj.
FIG. 7.—Branches of vessels near the posterior tibial artery ; ½ in. obj.

PLATE III.

FIG. 8.

FIG. 9.

Normal skull. Skull from case of acromegaly.

corpuscles, epithelial cells and granular detritus. The epithelial lining of this distended tubule was in part intact, and in part had desquamated, leaving a fibrous wall to the small cyst thus forming. We have, therefore, a slight interstitial and a very slight parenchymatous degeneration.

Sections of the *spleen* show a thickening of the capsule and a slight increase of connective tissue throughout, with a diminution of spleen pulp. The blood-sinuses have thickened walls and are filled with blood. The spleen, hence, shows chronic passive congestion.

In the testicle there are thick bands of fibrous tissue between the tubules. In comparatively few of the tubules are forming spermatozoa seen, and none are found in the tubes of the epididymis, which is lined with cells larger than those usually found here, and which do not show cilia.

A transverse section was made of the posterior tibial artery and the tissues surrounding it (Plate II., Fig. 7). While the artery itself shows only a very slight thickening of the intima, the *smaller vessels* show a marked thickening, due to a cellular increase in the intima, the lumen being much narrowed and in some places almost occluded. The arrangement of the proliferated tissue making up this thickened intima is in papillary projections between which are narrow slits, as seen in Plate II., Fig. 7.

The skin of the great toe shows a thick epidermal layer, thickened intima of the small arteries, and the *sweat glands* are lined with a layer of epithelium two or more cells deep, instead of a single layer of cells as is usual.

THE SKELETON. *The Skull* (Plate III., Figs. 8 and 9). The external and internal tables of the cranial bones are very thin, while the cancellous tissue of the occipital and frontal bones is much increased, making the bones as a whole somewhat thicker than usual. The middle fossa of the skull is very much deeper on the left than on the right side.

The supra-orbital ridges are much enlarged and prominent, while the glabella is very much enlarged, causing the forehead to appear very much to retreat, resembling the anthropoid apes. The metopic suture has entirely disappeared, as have also the sagittal and the lambdoid sutures. There are no Wormian bones present. The external occipital protuberance and the superior and inferior curved lines of the occipital bone are sharp and prominent. The vertical crest is very projecting and prominent. The mastoid processes are thin laterally, with sharp margins, the digastric fossæ being very deep. The para-mastoid processes are not marked. All of the crests and eminences on the base of the skull are more developed and prominent than usual. The glenoid cavities are very deep, but narrow from before backward, the tympanic plate being very large. The styloid processes are somewhat elongated and completely ossified. The right external auditory canal is considerably narrowed. The sella turcica is greatly enlarged, having a cavity of one and one-eighth inches antero-posteriorly, one and one-half inches laterally, and seven-eighths of an inch perpendicularly.

The sphenoidal sinus of the left side is larger than the right, and further forward than usual, being pushed forward by the enlarged cavity of the sella

turcica, which seems to have been largely due to actual bone-growth of the sella turcica; the right sphenoidal sinus is also pushed forward and much smaller than normal, and smaller than the left, owing to this same encroachment of the bones forming the sella turcica. Normally part of the upper wall of the sphenoidal sinus is the lesser wing of the sphenoid. In this specimen on the right side there is an interval of half an inch between the upper wall of the sinus and the lesser wing, the upper wall being a thin plate of bone. On the left side the same condition is found, but the distance from the lesser wing is one-quarter of an inch. On the right side a sinus is found of considerable size between the plates of the lesser wing of the sphenoid.

The optic groove has entirely disappeared. The anterior clinoid processes are very much enlarged. The handles of both hammer-bones are bent much from normal, and that of the right hammer almost to a right angle. The anterior and upper part of the auditory process is rough and enlarged, encroaching backward on the auditory canal. There is the same enlargement of the auditory process on the left side, but the auditory canal is not so narrowed. There is a marked spinous process at the lower end of the anterior malo-maxillary suture on both sides. The malar processes of the superior maxillary bones have extended laterally and have co-ossified almost completely with the malar bones, making the malar bones flat on their external aspect, instead of rounded as normal. The base of the orbit is quadrilateral in aspect, the infra-orbital margin being nearly horizontal, and the supra-orbital margin being less curved than usual; in other words, the orbit is greatly widened transversely. This condition is apparently almost entirely due to the enlargement of the malar processes of the superior maxillary bones.

The measurements of the orbits are the same, the transverse diameters being 49 mm., and the vertical diameters being 42 mm.

The lachrymal canals are much enlarged, with sharp and projecting margins at their upper orifices.

The posterior molar teeth on the upper jaw were found unerupted, the right being distorted in position; it lies horizontally in the jaw, with its crown facing outward, making a tuberosity on the external surface of the alveolar process, while its one fang is pushing into the mouth-cavity. The distance between the tuberosity of the one supra-maxillary to that of the other is 56 mm. The inside measurement, that is of the posterior part of the palate, is 40 mm. The nasal processes of the superior maxillary are enlarged and elongated, pushing the lower part of the nasal bone forward and upward, making a marked concavity on the bridge of the nose. The greatest transverse diameter of the anterior nares is 26 mm., while the greatest vertical diameter is 40 mm. The anterior nasal spine is much enlarged and prominent, with a very marked ridge continuing down from it to the alveolar process. The incisor fossæ are very deep. The maxillary sinuses (antra) are much enlarged, the left being greater than the right.

We therefore find the supra-maxillary bones as a whole to be greatly enlarged, the left somewhat more so than the right. The whole facial en-

PLATE IV.

FIG. 10.—Spinal column from case of acromegaly.

largement of the skull seems to be confined to the supra-maxillary and frontal bones.

Turning now to the inferior maxillary bone, we find the condyles to be elongated laterally and to project beyond the zygomatic processes. This enlargement seems to be due to the growth of the inner part of the condyles, which has thus pushed the rami outward. The transverse measurement of the left condyle is 37 mm., and the right 35 mm. The condyles are thin from before backward. The coronoid processes are not much enlarged, but are somewhat elongated. The angle of the jaw is quite obtuse. The rami are much lengthened, and the basilar border of the bone projects forward and is thick relatively to the rest of the bone. The mental region of this bone is greatly broadened. The width of the bone from angle to angle internally is 107 mm. (normal bone 93 mm.). From the outer edge of the one condyle to the outer edge of the other is 151 mm. (normal bone 120 mm.).

The Spinal Column (Plate IV., Fig. 10). The spine is very typical of acromegaly, showing a very marked kyphosis, the angle of which is in the upper dorsal region at the disk between the fifth and sixth dorsal vertebræ, and is an angle of about 80 degrees. This angle of kyphosis was so great that when the body lay on the table at autopsy the head could not touch the table, but stood up. This enormous kyphosis seems to be due to an absorption and loss of the intervertebral disks anteriorly rather than to a thinning of the anterior portions of the bodies or a thickening of the posterior portions of the bodies of the vertebræ.

A scoliosis is present, but not marked, with its convexity to the right.

The second, third, fourth, fifth, sixth, seventh, eighth, ninth, and tenth dorsal vertebræ are co-ossified by ossification of the anterior common ligament, there being marked exostoses at the position of the inter-vertebral disks. The second and third dorsal present anterior exostoses as wide as the bodies of the vertebræ. The second and third cervical vertebræ are ankylosed. The spinous processes are somewhat enlarged and show many projecting exostoses. The spinous processes of the fifth, sixth, seventh, eighth, and ninth dorsal vertebræ are partially co-ossified; the upper four apparently by an ossification of the supra-spinous ligament, while the eighth and ninth are joined by ossification of the inter-spinous ligament. The inter-spinous ligament of the eleventh and twelfth dorsal vertebræ is ossified, binding these vertebræ together.

All of the lateral processes are roughened and thickened by increased cellular tissue. In fact, all of the spinal bones have less compact tissue than normal, especially the bodies, which are very spongy.

The whole larynx, which was examined with the tongue and epiglottis in position, was greatly enlarged. The width of the base of the tongue, dorsal surface, just in front of the anterior pillars was three inches. And here I might say that all of the nerves of this region were enlarged. The greatest width laterally of the larynx was two and three-quarters inches.

The circumference of the cricoid cartilages was five and one-half inches.

The arytenoid cartilages were also enlarged. From the superior border of the cricoid cartilages to the top of arytenoid was seven-eighths of an inch, including bone and soft tissue—*i. e.*, vertical height of arytenoid. All of the cartilages show more or less calcification.

Below the vocal cords the larynx was much enlarged, forming a widened space. The distance between the vocal cords behind was less than usual, owing to the enlargement of the soft tissues; this in spite of the larynx itself being enlarged.

The epiglottis is very prone.

The hyoid bone is horseshoe-shaped, the greater cornua looking toward each other rather than away from each other, as normal.

The hyoid bone from tip to tip around its anterior convexity measured seven inches.

The upper tracheal rings are calcified.

The sternum is very greatly enlarged, measuring 200 mm. in length, with the greatest width of the gladiolus of 50 mm. and the width of the manubrium 78 mm. The angle between the manubrium and gladiolus is more projecting than usual. The manubrium and the first rib on each side are co-ossified. The sternum is thickened in its entire extent. The ensiform appendix is 65 mm. long, and is completely ossified, and is co-ossified with the sternum. There is a large foramen in the centre of the appendix.

The costal cartilages are ossified and are fully a third longer than usual. The sixth, seventh, and eight costal cartilages are co-ossified at interchondral joints on the left side, but are not co-ossified on the right.

The ribs are broadened, thickened, and elongated with all curvatures lessened. The seventh rib measures 435 mm.

The clavicles (Plate V., Fig. 11) are enormously enlarged, being increased at least one-half in size. They are rather more curved than normal, with the margins of the articular surfaces prominent and extended. They present very large surfaces for articulation with the sternum.

The acromial extremity is very greatly enlarged.

The conoid tubercles and trapezoid ridges are very much enlarged.

The scapulæ are markedly enlarged in every way except in length, and are distinctly broadened.

The glenoid cavities are somewhat deep and rough, with exostoses at the edges.

The spines are very large.

The heads of the humeri (Plate VI., Fig. 12) show roughened articular surfaces and an increase in bone, due to the ossification of the articular cartilages.

The deltoid ridges are enormously enlarged, evidently due to the ossification of the tendon of the deltoid. The same condition is true of the anterior bicipital ridge at the site of the attachment of the pectoralis major muscle.

The external epicondylar ridge is very much enlarged and projecting.

PLATE V.

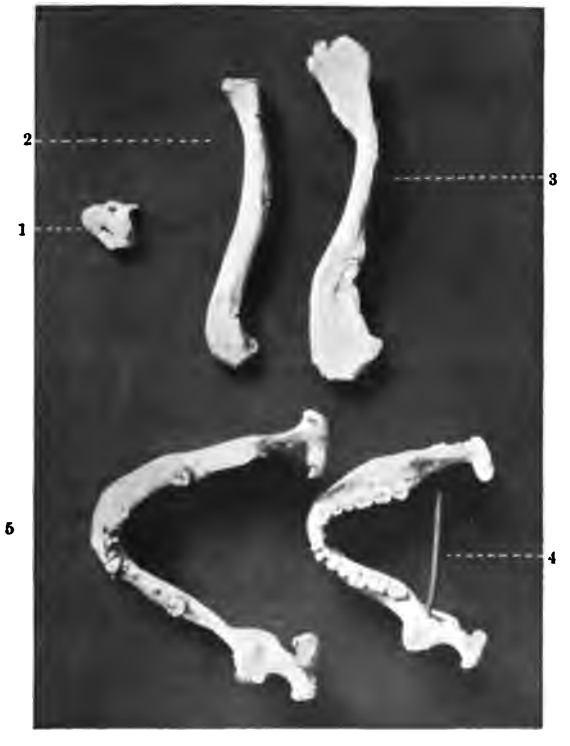


FIG. 11.

1. Distal phalanx of toe.
2. Normal clavicle.
3. Clavicle from case of acromegaly.
4. Normal inferior maxilla.
5. Inferior maxilla from case of acromegaly.

PLATE VI.

FIG. 12.

Normal humerus. Humerus from case of acromegaly.

PLATE VII.

FIG. 13.—Skiagraph of right forearm and wrist from case of acromegaly.

PLATE VIII.

FIG. 14.—Skiagraph of right hand from case of acromegaly.

The radii do not show roughened articular surfaces.

The interosseous ridge is very sharp and projecting. The lower ends of the radii are not enlarged, but have many bony protuberances.

The lower articular surfaces are widened by a growth of bone at the anterior margins.

The ulnar bones are enlarged at their upper ends, and are rough and irregular in all the details of their upper extremity. The articular surfaces are increased in extent by the growth of bone at their margins, especially at the coronoid process. This surface is also more concave and roughened than normal. The interosseous borders are enlarged. The lower extremity of the ulnar bone is flattened and not enlarged.

The articular surfaces encroach upon the normal depression between the head and styloid process; it is again an instance of the extending of articular surfaces by ossifications in cartilage.

The nutrient canals are not enlarged, but the articular canal of the upper extremity of the ulna is enlarged.

All of the bones of the carpus (Plate VII., Fig. 13) are very much enlarged.

The metacarpal bones (Plate VIII., Fig. 14) are all enlarged, especially at their upper extremities. The metacarpal bones of the thumb are widened, not only at their extremities but in their shafts, due to a laying on of bone at the lateral ridges. The articular surfaces of these bones are also greatly enlarged.

The phalanges of the hand (proximal and middle) are not much enlarged, except that the ridges on these bones are more prominent than usual.

The distal phalanges show enlargement of both extremities, with a great deal of increase in spongy roughness at the ungual end. This end is broadened and thickened, due largely to ossification on the pulp surfaces.

The Pelvis. The whole of the iliac bones are enlarged.

The crests of the ilia are greatly thickened, and are not as sinuous as usual, while the iliac fossæ are more flattened than normal, apparently due to a spreading out of the ilia. The bones in the expanded portion of the ilia are thin. The distance from one anterior spine to the other is 295 mm.

The acetabular cavities are enlarged and very deep, with very prominent margins. The normal depression at the bottom of these cavities is three-quarters filled with an osseous plate, and the entire articular surface is rough.

The symphyses of the sacrum and ilia are partially co-ossified anteriorly. The sacrum is broad and enlarged, due to an increase of the lateral masses. The concavity of the sacrum is somewhat increased. The coccyx and sacrum were not co-ossified.

The pubic bones are thin, the obturator foramina being markedly increased in size. The spines of the pubes are enlarged, especially on the left side.

The horizontal rami are thin and narrowed, and the bodies are thinner than normal. The distance from the symphyses anteriorly to the ilio-pubal eminence is increased, measuring 90 mm. The pubic bones have, therefore, lost in substance but have grown in extent.

In the left hip-joint in front anteriorly to the neck, just below the head of the femur, was found a loose irregular calcification one inch in diameter. The femurs are large with very large heads, the cartilages covering the heads are rough, and the articular lamellæ are rough and porous. The great trochanters are very rough. The articular lamellæ of the condyles are rough and porous.

The tibiæ are not much enlarged; neither are the fibulæ, though the ridges of the fibulæ are prominent.

The patellæ are enlarged and show projecting processes and exostoses from the upper and posterior borders. The margins of the articular surfaces show new bone-growth.

The os calcis is enlarged as a whole, but especially at its posterior surface at the attachment of the tendo-Achillis, another instance of the ossification of a tendon. The whole bone is roughly irregular and nodular.

All of the bones of the tarsus are enlarged, showing enlargement of their articular surfaces by the laying on of bone, and showing roughening of their ridges.

The sesamoid bones are not increased in number.

The metatarsal bones of the first and second phalanges of the feet are not enlarged, but the ridges are more marked and prominent than usual.

The third phalanges are enlarged at both extremities, with a growth of spongy bone, not only at their distal ends, but at their proximal, with extension of lateral portions (see Plate V., Fig. 11) toward the distal ends, causing actual enclosed foramina on some of the bones, and deep notches in others, the majority, however, being closed foramina. The distal ends of these phalanges curve upward.

I am indebted to Dr. H. B. Ferris, Professor of Anatomy at Yale, for his careful supervision of the above detailed description of the changes from normal in the bones of this skeleton.

Points of Special Interest in this Case.

The thyroid and the thoracic thyroid glands were both sent to Prof. R. H. Chittenden for chemical examination, accompanied by a positive statement that this man had received no iodine-carrying drug in at least six years.

Dr. L. B. Mendel, first assistant in Prof. Chittenden's laboratory, later sent me the following report, namely, that the thyroid gland contained but 0.15 of a milligramme of iodine as a maximum content for the total gland. This amount of iodine is, therefore, only one-twentieth of the amount which Baumann claimed the normal thyroid gland of the adult should contain—*i. e.*, 3 milligrammes; while Weiss, from an analysis of fifty human thyroids, claims that the normal adult gland should contain 4 milligrammes.

Dr. Mendel also reports, in regard to the thoracic gland found in this case, that he not only found iodine in the gland, but in large amount, namely, 6 milligrammes as the content of the whole gland, or twice as much as is contained in the normal thyroid. He finds by careful analysis of different portions of this thoracic gland, that the whole of the iodine is contained in the cortical, or "more porous portion," while there is no iodine in the central, or "more compact and homogeneous" portion. This coincides exactly with the microscopical sections of this gland, which show the outer portion to be glandular and the central portion of the gland to be of connective tissue. (Plate II., Fig. 6.)

So far as we are aware, this is the first time that iodine has been found in an auxiliary thyroid gland. It is needless to say that the very best possible control-tests were made. All of the preservative fluids and sections of other organs from the same jars, and the muscle-tissue around the glands, were all tested for iodine, with absolutely negative results.

We will turn now for a few minutes to the description of this case reported by me in 1892, in which, owing to the occasional small amounts of albumin being found in the urine "the kidneys were stated in all probability to be slightly damaged." The albumin was never found in any amount except on the day before death, and was absent, as were also casts, during the last few weeks of his sickness. Sugar was found once in small amount, about eight months before death. He complained of irregular abdominal pain, and the autopsy showed that there were a number of peritoneal adhesions.

The condition of the handle of the hammer of the right ear, discovered and remarked upon by Dr. H. L. Swain in 1892, was abundantly substantiated by the condition of the bone found at autopsy, namely, with its handle bent almost to a right angle.

In 1892 I wrote the following in regard to the pituitary body of this patient:

"Have we in this case the symptoms of an enlarged pituitary body? Yes; the enlarging gland would naturally tend to press in the direction of the least resistance. The least resistance can only be out of the sella turcica, either laterally toward the cavernous grooves, or upward and forward toward the middle clinoid processes. The excess of pressure in either direction will depend upon the bony environments of the sella turcica, and in either case

the enlarging pituitary body reaches bloodvessels. If the bone formation of the sella turcica is such that the first pressure is exerted laterally, the internal carotids and cavernous sinuses are pressed upon and the soft walled sinus is most affected. By this pressure we then have a venous hum in the ears, and the pressure being continuous the tinnitus will be continuous. The difference in the intensity of the ringing in the ears might be due to an asymmetrical enlargement of the pituitary gland, but is more probably due to the formation of the sella turcica allowing freer passage of the gland on one side than on the other. The middle clinoid process being more prominent on the one side than on the other—a frequent condition—the enlarged gland would press more on the opposite bloodvessels. This is probably the condition in this case."

The above inference has certainly been well borne out by the conditions found at autopsy. A small-celled tumor-growth containing a cyst occupied the sella turcica; this could not press upward owing to the bony formation of this sella turcica, but did grow laterally and much more on the right side. This tumor-growth not only pressed upon the right cavernous sinus, but also this small-celled growth had grown into the wall of the sinus, almost occluding it. The same was true, but in much less degree, of the left cavernous sinus. This then gives the cause of the constant venous buzzing or humming of the ears, which from the loss of gravity to these veins would be worse on lying down.

In 1888 this man showed decided symptoms of brain pressure, and at that time the diagnosis of "brain tumor" was made; the acute symptoms (however, lasting only about one month) I stated in 1892 to have been probably "due to the first pressure of the enlarging pituitary body on the bloodvessels," which gave him "continuous head pain and caused him to have deranged spells."

In 1892 I described the pain, which he said he constantly had and referred to the top of the head at the region of the anterior fontanelle which is directly perpendicular to the sella turcica, and about the size of the thumb tip, and also referred down the right side of his nose. I attributed this to the pressure of the enlarged pituitary body. It is interesting now to note that directly under this spot was a plate of ossification in the dura mater.

This man died by syncope, and unexpectedly, as Marie claimed to be typical of death from acromegaly. This was evidently due, as was the œdema of the feet and legs, to his weak heart. The heart con-

tained connective tissue between its fibres, and some fatty globules; hence, though the heart was enormous in bulk it was weak in action, as was also shown by the auscultatory sounds.

The interesting factors in this case might be summed up as follows:

1. The liver weighed seven pounds, two ounces; a normal liver three to four pounds.
2. The spleen weighed two pounds, four ounces; a normal spleen weighs seven ounces.
3. The heart weighed two pounds, nine ounces, one of the largest hearts on record; a normal heart weighs from ten to twelve ounces.
4. A thoracic thyroid gland weighing thirty-six and one-half grammes, containing a large amount of iodine.
5. The thyroid gland weighed over 101 grammes, with almost absence of iodine; the normal thyroid weighs from thirty to sixty grammes.
6. General increase of intima of all bloodvessels.
7. Increase of connective tissue in the heart.
8. Small-celled growth in sella turcica, and encroaching upon cavernous sinus, and same growth in small tumors attached to base of brain (sarcomatous?).
9. Sweat-glands lined with extra layer of epithelium.
10. Large sella turcica.
11. Large superior and inferior maxillary bones.
12. Clavicles enormous.
13. Spine typical of acromegaly.
14. Carpus enlarged.
15. Tarsus enlarged.
16. End-phalanges of feet show peculiar bone-growth.

ON THE OCCURRENCE OF THE FAT-SPLITTING FERMENT IN PERITONEAL FAT NECROSES AND THE HISTOLOGY OF THESE LESIONS.

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The relation which exists between certain diseases of the pancreas and fat-necrosis has been emphasized, especially by Fitz, in his comprehensive studies of pancreatitis. According to this author,[1] disseminated fat-necrosis in the peritoneal cavity is comparatively infrequent in the suppurative form of pancreatitis, while it is not uncommon and is relatively frequent in the hemorrhagic and gangrenous varieties respectively. Balser,[2] who first directed attention to this condition, of which he gave a full description, found it five times out of twenty-five autopsies, either within the interacinous tissues of the pancreas or in the adjacent or distant adipose tissues. Since that time fat-necrosis has been observed by a large number of pathologists in cases in which gross disease of the pancreas has been wanting at autopsy. In these instances the necroses are limited, as a rule, to the immediate neighborhood of the gland, although at other times they have been found more widely disseminated when such disease of the pancreas existed. Still more recently, and now that acute suppurative or necrotic pancreatitis has become a field for surgical interference, the condition has been encountered at the operating-table.

The coincidence of disease of the pancreas with the occurrence of fat-necrosis in the peritoneum on the one hand, and the proximity of the necrotic areas to the pancreas, on the other hand, lent support to

[1] Acute Pancreatitis. The Middleton-Goldsmith Lecture, 1889.
[2] Virchow's Archiv, 1882, xc. p. 520.

the view, quite early advanced, that a relation of cause and effect must exist between the gland and this pathological process. The first attempt which may be regarded as at all successful to prove this assumption by experimental means was made by Langerhans.[1]

In his studies[2] of the histology of the lesions he had satisfied himself that a decomposition of the fat-molecule had taken place, liberating the fatty acids which, after a time, combined with calcium to form insoluble lime soaps. He, therefore, experimented by injecting sterile pulp of the fresh pancreas into the perirenal tissues of a rabbit, with the result of setting up an inflammatory process in which evidences of fat-necrosis were detected. In his repetitions of this procedure he did not always obtain similar results; but, although he could claim only a single successful experiment out of twelve attempts, he nevertheless felt justified in considering that "the fat-splitting ferment, by acting directly upon the tissues, sets up a suppurative inflammation, while its less intense action brings about a decomposition of the oil-drops within the fat-cells, resulting in fat-necrosis."

The experiments which have followed those of Langerhans have consisted in the introduction of portions of fresh pancreas into the peritoneal cavity of rabbits and dogs, the isolation of the pancreas from its main veins so as to bring about the production of passive congestion, thus favoring, as it is thought, the passage of the secretion into the blood, and the separation of one-third to one-half of the head of the pancreas from the tail, which is then permitted to pour its secretion directly into the peritoneal cavity. These experiments, which have been more or less successful, have been made by Dettmer,[3] Hildebrand,[4] Körte,[5] and Williams.[6] The facts which they established are: (1) the secretion of the pancreas may enter the peritoneal cavity without setting up diffuse inflammation, a conclusion previously arrived at by Senn; (2) in a certain number of instances the free, sterile pancreas or the pancreatic secretion causes

[1] Experimenteller Beitrag zur Fettgewebsnekrose, Virchow's Festschrift, 1891.

[2] Virchow's Archiv, 1890, cxxii. p. 252,

[3] Experimenteller Beitrag zur Lehre von den bei Pancreatitis hæmorrhagica beobachteten Fettgewebsnekrosen und Blutungen. Inaug. Diss., Göttingen, 1895.

[4] Ueber Experimente am Pancreas zur Erzeugung von Fettnekrosen, Centralb. fur Chirurgie, 1895, xxii. p. 297.

[5] Berliner Klinik, 1896, Heft 102.

[6] Boston Medical and Surgical Journal, i., 1897.

focal fat-necrosis; and (3) the element of infection plays an insignificant, if not an entirely unessential, part.

In order to connect more certainly the pathogenic action of the pancreatic secretion with the fat-splitting ferment, and in view of the fact that the ferment itself is not obtainable in a form suitable for experiment, the effects of trypsin were tried. It was found, especially by Dettmer,[1] that pure trypsin caused a sero-hemorrhagic exudation into the peritoneal cavity, but was without power to set up fat-necrosis. The diastatic ferment having already been excluded, it was regarded as highly probable that the fat-splitting ferment was the active agent.

My present studies have dealt with two problems. The first was the demonstration of the presence of the fat-splitting ferment in the areas of necrosis, and its absence from the normal fat in a suitable human case. The second was to confirm this observation by making similar tests upon animals in which fat-necrosis had been experimentally produced. In the second series of cases experiments were made with a view of determining how long the ferment remained in the tissues in demonstrable conditions or amounts.

I may say in this place that the successful experimental lesions were subjected to microscopical study, and the existence of necrosis was proven. The histology of the experimental lesions is also considered in this communication.

The method which was uniformly followed in the demonstration of the ferment is essentially that of Claude Bernard, for the details and practical carrying out of which I am indebted to Dr. Abel, to whom I wish to express my obligations. It consists in preparing a perfectly neutral fat, which I did from fresh butter by dissolving it in ether, adding a few drops of NaHO, and washing out with successive quantities of distilled water. The separated ethereal solution of neutral butter was evaporated over a water-bath, and the tests were made at once. For this purpose, in each instance, I employed (1) a piece of the pancreas itself, (2) one or more focal necroses, and (3) a piece of adipose tissue equal in size to the pancreas or necroses taken at a distance from the latter. The pieces of tissue were placed in 90 per cent. pure alcohol for from one-half to two hours, pressed

[1] Op. cit.

in filter-paper, reimmersed in the alcohol for a short period, again pressed, and then allowed to become air-dry. They were then cut into morsels which were incorporated with the natural fat in watch-crystals, which were then covered and placed in the thermostat at the body-temperature.

For the demonstration of the action of the ferment two methods were employed. The first was the detection of the liberated fatty acids by the sense of smell. The second consisted in dissolving the butter, etc., in pure absolute alcohol and adding tincture of litmus to the alcoholic solution. It was quite remarkable how well the two tests agreed with each other. The exact details will be given in the individual protocols.

It would seem that the reaction takes place quickly if the ferment is present in an active condition. In not a few instances a distinct and even marked reaction was obtained within six minutes from the time of placing the watch-crystals in the thermostat.

The animals used for experiments were cats and dogs. The former appeared to be better adapted for the purpose. The operations consisted of (1) ligation of all the veins proceeding from the pancreas, which was quickly followed by a vivid congestion of the gland and the laceration of the organ by means of a sharp hook; (2) the same operation, in addition to which a strong ligature was thrown about the splenic half of the organ; (3) the ligation of the veins, tying off of the splenic half and section beyond ligature; (4) the isolation of the duct of Wirsung, this ligation where it entered the duodenum and section. The effects of congestion alone were tried in two cases without marked success.

The object in these experiments was to produce necrosis at a distance from the gland which would serve for the tests mentioned. It was also considered desirable to avoid all infection of the peritoneal cavity. The most satisfactory results were obtained after ligating the veins and lacerating the pancreas. Tying off one-half of the organ was soon abandoned, inasmuch as it was found that the ligated part sometimes suppurated and the necroses were not more extensive than in other cases. Cutting the duct of Wirsung (one case) did not lead to extensive necroses. The focal areas were found in the pancreas and mesenteric fat close to the site of operation, and were small in size. The duct in the cat is hardly larger than a capillary

tube, and, it is believed, quickly becomes obliterated after section. By the use of rigid surgical precautions, except in two cases of suppuration about the ligature around the pancreas, in one instance only (a dog) was a general peritonitis encountered. Notwithstanding a sero-purulent exudate in the abdominal cavity, this animal appeared to be in perfect health when killed three days after operation.

The necroses varied in extent. They were always to be detected about the pancreas, in the interacinous and peripancreatic adipose tissue. They were usually present in the fat of the gastro-hepatic omentum, and more variably in the great omentum and mesenteric fat. When in the mesentery the necroses were apt to be the duodenal and upper jejunal portions and in that of the descending colon. They were never discovered in the perirenal tissue. Wherever adhesion took place between the omentum and the lacerations on the surface of the pancreas there fat-necroses were always found.

In size the necroses varied from a pin's head or less to a pea. The smaller ones were yellow or white and opaque, the larger often hemorrhagic. The latter were usually selected for the tests.

With one exception all the animals were killed, chloroform being used for this purpose. The animal which succumbed spontaneously was a full-grown but rather poorly nourished cat, which died two days after the operation. There were in this instance many areas of necrosis in the pancreas and mesentery and fewer in the omentum. In part they were hemorrhagic. The other animals were killed on the second, third, fourth, sixth, and eighth days respectively. Positive reactions for the ferments were obtained in all, except the two longest periods mentioned.

In order to determine whether in the long periods the ferments were present at an earlier date only to disappear later on, the animals were subjected to a second operation (Protocols C, D, and E), at which time the necrotic foci were excised and tested, the peritoneal cavity being again closed. These tests were made on the third day after the first operation. The cats were killed on the sixth and eighth days respectively. The first tests were positive; the second negative in all instances.

When we come to consider the histology of the experimental lesions we shall find that a great difference exists in those of the first three and those of the sixth and eighth days. While in the

former the process is very acute, in others the evidences of cicatrization are most pronounced.

The conclusions which may be drawn from the foregoing observations are: (1) in peritoneal fat-necrosis the fat-splitting ferment is demonstrable at certain stages of the pathological process; (2) it is present in greatest amount in the early stages, and may disappear in the later ones when healing is well advanced; (3) although it cannot be affirmed that steapsin is the direct cause of the necrosis of tissue, such an assumption is rendered highly probable by its constant occurrence in the diseased areas, its absence from the healthy fat, and the nature of the pathological changes; (4) the escape of the pancreatic secretion into the peri- and parapancreatic tissues is the origin of the necroses, and this escape is facilitated chiefly by lesions of the pancreas itself, and also by disturbances in its circulation.

That necrosis of fat-cells may result from other causes is certainly not excluded by these findings. What is the genesis of similar lesions found in the marrow of the bones by Ponfick,[1] in the subcutaneous fat (Chiari), and pericardial fat (Balzer, Chiari), is not immediately apparent. That micro-organisms may, in these cases, play a part is, in my opinion, very probable indeed. Ponfick's case was one of empyema in which, beside the lesions in the medulla of the bones, areas of softening not due to vascular occlusion, existed in the myocardium.

The histology of the fat-necrosis as it occurs in human beings has been studied by Ponfick, Balzer, Fitz, Chiari,[2] and especially by Langerhans.[3] The experimental lesions also have been subjected to microscopical examination and compared with those found in man. The main facts to be gleaned from these observations are as follows: The pathological process begins with a decomposition of the neutral fat contained within the fat cells; the fluid constituents are eliminated and the solid fatty acid crystals remain behind. These, after a time, unite with calcium to form insoluble lime salts. The pathological products are found within the protoplasm of cells whose nuclei have already lost or are preparing to lose their affinity for staining-agents. The general form and character of the cells are

[1] Virchow's Archiv, lvi. 1872, p. 541.
[2] Prager medicinische Wochenschrift, viii. 1883.
[3] Virchow's Archiv, cxxii. 1890, p. 252.

retained for a time; but in later stages the lime compounds occur free under the form of granules, rings, and hyaline masses (Schollen) which as a whole appear white and non-transparent. Thus it happens that a small number of cells, a whole lobule of adipose tissue, or even several adjacent lobules, may give rise to a necrotic focus which now becomes the seat of a reactive (demarcating?) inflammation.

Pathological alterations within the bloodvessels may be slight or entirely wanting, and are, at best, so inconstant and variable as to be excluded as representing the exciting cause of the lesions. In the same way the part played by micro-organisms can be only an insignificant one, and is probably limited to an occasional instance. At any rate, all evidences of constancy of relationship between bacteria and the necrotic foci are thus far wanting.

One of the objects of my study of the histology of the experimental lesions was to compare them with those occurring in the course of disease in man. As a basis for this comparison two human cases were studied, in one of which the necrotic lesions were widely disseminated (Protocol A), and in the other were nearly limited to the pancreas and peripancreatic tissue (Protocol B). In the first case only was the fat-splitting ferment demonstrated in the necroses; in the other no attempt was made to detect it owing to the intimate association of the lesions with the pancreas. Still another purpose of this study was the determination of the changes which take place in the tissues coincidently with the disappearance of the ferment from the necrotic foci. The observations upon this point may be taken as a contribution to our knowledge of the healing of fat-necroses.

There is little difficulty in the human cases mentioned in confirming the results of Langerhans' researches. In addition it is to be noted that lesions may come under observation early, before the lime compounds have formed, in which case, beside the changes peculiar to fat necroses, those of an acute inflammatory nature are also present. This fact is true of one of our cases (Protocol A), in which none of the disseminated foci of necroses had been incrustrated with lime. The white, opaque, central mass is composed of confluent cells, derived from the adipose tissue, the individual outlines of which have been lost and in which nuclei, either complete or as fragments,

are entirely wanting, but which are occupied by fatty acid crystals. The addition of concentrated sulphuric acid and then water does not bring these cyrstals out more distinctly, but quickly decomposes the fat in the unaltered cells, causing a separation of an abundance of crystalline fatty acids. At the end of twenty-four hours no further change has taken place; sulphate of calcium crystals have entirely failed to make their appearance.

Just outside the completely necrotic focus is a zone of infiltration in which cells and fragments of cells and nuclei are found in large amounts. This presents somewhat heterogeneous characteristics; it constitutes in part the zone of reaction—demarcating inflammation—and encloses many ring-shaped and globular hyaline bodies which are characterized further by their peculiarly intense staining with hematoxylon. Among the foreign elements in this mantle, polymorphonuclear leucocytes and cells of the lymphoid type are to be distinguished. Beginning at this point and extending for a variable, but often considerable, distance into the surrounding tissue, there are evidences of an inflammatory invasion consisting of œdema, hemorrhage, and especially of fibrin. Many swollen and nereotic cells (emigrated and tissue elements) are present in this part. It is noticeable that the rich network of fibrin tends to extend along the connective tissue septa against which many of the necrotic foci abut. This diffusion of the simple inflammatory lesions, in contradistinction to the definitely circumscribed nature of the specic necrotic areas, is a remarkable feature of the pathological process.

Evidences of proliferation of the fixed tissues are abundant; even in such early stages as just described they are discernible; but later (Protocol B) they are much more marked. There is nothing peculiar about the manner of this new growth, except that it is peripheral. The necrotic centres do not become invaded but gradually shrink, and finally would appear to be completely replaced by connective tissue. At the time of great activity of the tissues the acute inflammatory process is no longer to be made out; red blood-corpuscles, serum, and fibrin have disappeared.

The pancreas itself suffers in two ways: it undergoes necrosis in the same way as the adipose tissue. This is observed on the surface (extension by continuity) and deeper down near the interlobular connective-tissue bands. Again, it is invaded by a new growth of con-

nective tissue not limited strictly to the fields of necrosis. Finally, and in this way, small nodules characteristic of interstitial pancreatitis, with loss of parenchyma, come to be formed.

The acute lesions of the experimental cases approach very closely to the corresponding lesions in man, while the older ones in animals pass through more typical stages of healing, and apparently also in a shorter period of time. The central mass of the necrotic cells is indistinguishable in the two forms, while the peripheral zone of infiltration is, perhaps, greater in the experimental cases. The elements composing this zone differ somewhat. The great majority of preserved cells exhibit single, deeply staining nuclei. Fibrin appears somewhat variably; necroses seventy-two hours old (Protocol C) may be devoid of it, while again it may be abundant in about the same period or even later (Protocols D and E). The pancreas itself may suffer severely or may escape entirely. In the first instance large necroses exist within the parenchyma. The venous radicles are occupied by light fibrinous thrombi.

Cicatrization is already under way on the sixth day (Protocol D), and on the eighth it is well advanced (Protocol C). The new cells are developed at the periphery of the focus of necrosis, the proliferation extending well beyond the immediate site of injury. The necrotic area gradually shrinks, becoming smaller and smaller without being invaded to any extent either by wandering or fixed cells. Multinuclear (giant) cells occur either at the most recent edge next the necrosis or at some distance in the adipose tissue. At this time (eighth day) the outermost zone of granulation tissue is already fibrillated. If the area has been hemorrhagic, blood pigment (hæmatoidin) is still present and is enclosed in the new cells.

The central mass of necrosis is not completely calcareous, and it is exceptional to obtain the micro-chemical reaction for calcium. From the following protocols more detailed information may be obtained:

PROTOCOL A. Woman, aged fifty years. Well nourished; well-developed panniculus. Sudden death; symptoms of œdema of the lungs. Anatomical diagnosis: gallstones in common duct; dilatation of duct above the concretions; dilatation and distention of gall-bladder; jaundice. Disseminated peritoneal fat-necroses. Moderate chronic diffuse nephritis.

The under surface of the omentum shows a considerable number of foci of

fat-necroses, surrounded by hemorrhagic or hyperæmic zones. The nearer the pancreas is approached the more numerous become these foci. The greatest number in the omental fat are found on the left side, passing down almost to the crest of the ilium. Where the necroses are most abundant, near the pancreas, adhesions, easy to break down, exist between this organ and the omentum. Similar adhesions between the omental foci and the abdominal wall, near the iliac crest, are met with, and hemorrhage has taken place freely into the pouch formed in this manner. The pancreatic interstitial fat, especially in the splenic portion and the mesentery, also shows foci of necrosis. The pancreatic duct is not dilated; its contents are, however, thick and opaque. The lymphatic glands in the neighborhood of the pancreas are swollen and reddened; the general peritoneal glands appear to be normal.

The following tissues were tested, in the manner described, for the fat-splitting ferment: (*a*) a bit of dog's pancreas; (*b*) a bit of pancreas from this case; controls: (*c*) several of the focal necroses with the adipose tissue immediately surrounding them; (*d*) adipose tissue from a distance. Result: positive reaction in ten minutes in all except *d*; more marked reactions at the end of fifty minutes. No development of rancidity in *d* at the end of the experiments after one hour.

Cultures made from the viscera after returning to the laboratory (the autopsy having been made at a distance) gave the following results: heart's blood, liver, and gallstones were negative. Pancreas, spleen, fat about the pancreas and kidneys gave a bacillus belonging to the group of B. coli communis.

PROTOCOL B. Man, aged fifty-six years. Heavy periodical drinker. Large, well developed, obese. Anatomical diagnosis: biliary (hypertrophic) cirrhosis of liver; ascites; chronic diffuse nephritis; lobular pneumonia; general passive congestion of viscera; multiple foci of fat-necrosis in the pancreas.

The pancreas is large, gray in color, and firm in consistence. There exist just beneath the capsule several whitish areas, the largest not exceeding 5 mm. in extent, which proved to be fat-necroses. They are more numerous in the substance of the organ, where they appear in the form of lines and squares, and often contain a putty-like material. The addition of H_2SO_4 and water to this material yields, after a time, gypsum crystals. The ferment was not sought in these foci, owing to their proximity to the pancreatic tissue.

PROTOCOL C. March 30th, noon, operated upon two cats, as follows: No. 1, tied off the largest veins only, excepting omental branches; No. 2, tied off all the veins which could be found; lacerated pancreas with a sharp hook. Three days later (April 3d, noon), cat No. 1 opened under ether anæsthesia; a number of small, white, opaque necroses existed in the omentum near the pancreas; somewhat larger ones present in the pancreas itself. Clean peritoneum. A bit of the fat containing three small necroses (not

exceeding 2 mm. each) excised; abdominal cavity closed. Cat No. 2 opened in the same manner. Peritoneum clean; omentum free except at one point where it is tucked over a laceration in the pancreas. Numerous fat-necroses in the omentum and in the fat about the pancreas; the individual ones are much larger than those in No. 1. Two focal fat-necroses excised; one of these represents one-half of a large omental focus, the other half being left for a future experiment. A single hemorrhagic node free from visible necrosis also excised from the omentum. Abdominal cavity closed. Tests for the ferment: No. 1 showed no reaction to the sense of smell in one hour; very faint reaction to litmus. Butter control negative. No. 2: two necroses tested separately; hemorrhagic area also tested. The necroses reacted promptly both by odor and to litmus. Hemorrhagic nodes gave no reaction. April 8th (eight days after first operation) both animals chloroformed. No. 1: no necroses to be found except in and near the pancreas about the ligature. No. 2: clean peritoneum; the foci of necrosis fewer in number and reduced in size. A number of small ones (pin-point to pin-head) are found in the omentum. The remaining half of the excised necrosis is reduced to the size of a canary-seed, and is firm and white. Tests for ferment: (*a*) one focus, 1.5 x 2 mm., from the lesser omentum; (*b*) a piece of the great omentum having a number of necroses side by side; (*c*) the remains of the partly excised necrosis; (*d*) bit of the pancreas. Results: no reaction either to sense of smell or to litmus in *a*, *b*, and *c*. Positive reaction (five minutes) in *d*.

PROTOCOL D. April 22, 10 A.M., operated as follows: Cat No. 1; veins tied; pancreas lacerated. April 24, 4 P.M. (after fifty-four hours), peritoneum opened under ether narcosis. A number of focal areas of necrosis in or near the pancreas; other smaller ones at a greater distance. Two nodules excised, (*a*) hemorrhagic from the omentum, (*b*) opaque area from the capsule of the pancreas. Test for ferment: (*a*) faint reaction of rancidity and to litmus; (*b*) stronger and marked reactions. April 28th (after six days) animal chloroformed. No distinct nodules in the omentum; several flat, white areas in the pancreas. No reaction from the former.

No. 2. Smaller, poorly nourished cat. Pancreas lacerated without tying off of veins. Died during night of April 23d. Autopsy April 24th. Peritoneum clean; the edges of the wound sticky, but no pus found. Many areas of focal necrosis in pancreas, mesentery, and omentum. Bacteriological examination of cover-slips from the wound showed a few doubtful cocci; cultures from peritoneal cavity sterile. Ferment in necroses (two tests) and in pancreas (control).

PROTOCOL E. May 11th, noon, operated on two cats as follows: No. 1; half grown; tied off the veins and lacerated the pancreas. May 13th, animal died. No necroses in the omental or mesenteric fat. Several small, opaque points near the pancreas. No tests. Cause of death not made out. No. 2; full-grown animal; tying of veins, laceration of pancreas, and ligation of splenic half of the organ. Section of the pancreas beyond the ligature,

permitting the splenic half, with its ducts, to be in free communication with the peritoneal cavity. May 14th, noon, under ether anæsthesia opened the abdomen and removed (*a*) a bit of adipose tissue from the omentum; (*b*) a focus of necrosis from this situation; (*c*) necrosis in the pancreas; *a* and *b* tested for the ferment. Results: from adipose tissue no reaction; from necrosis, positive reaction; *c* reserved for histological study. May 17th, cat chloroformed. External wound suppurating; peritoneal cavity clean. A number of small, opaque foci of necrosis in the omentum. Owing to their small size, several were united for the test. A piece of pancreas from the animal used as a control. The necroses had no reaction; the pancreas gave positive results. The largest necrotic area was studied histologically.

PROTOCOL F. Cat; operation March 18th. Veins ligated; ligature about splenic portion of pancreas. Chloroformed March 23d. The ligature about the pancreas nearly severed the organ. It was covered with a small quantity of sticky, pus-like material. Peritoneum otherwise clean. Many foci of necrosis, the greatest number being near the pancreas on the splenic side. They involve the omental fat over the stomach and its free portion, the mesentery, and the substance of the pancreas. Positive reactions for the ferment from the pancreas and from the necroses from omentum and mesentery. No reaction from adipose tissue alone.

PROTOCOL G. Same operation as and similar results to those in F.

PROTOCOL H. April 8th, 11 A.M. Full-grown cat. Isolation of the duct of Wirsung at its entrance into the duodenum; ligation at the intestine and section. A small drop of clear fluid immediately escaped from the proximal end. Animal chloroformed April 12th, 10 A.M. Peritoneal cavity clean. No general foci of necrosis. On the other hand, necroses exist about the ligature, in the fat between the duodenum and the pancreas, extending along the sheaths of the bile-duct and the bloodvessels toward the liver. Duct dilated. No test for the ferment.

PROTOCOL I. Small black dog. Operation March 16th. Ligation of veins, ligation of the splenic half, and laceration of the pancreas. Chloroformed March 22d. External wound granulating; peritoneum clean. The largest area of necrosis is 6 cm. from the pylorus, and extends from the pancreas to the intestines, following the ligated bloodvessels. At the intestine (duodenum) the necrosis spreads in the form of fine lines over the serosa. Similar white lines, showing nodosities and suggesting strings of beads, run over the pancreas itself. Test: (*a*) fat about kidney free from necrosis; (*b*) pancreas; (*c*) fat with lines of necrosis from duodenum. Reaction in from six to eight minutes in *b* and *c*. No reaction in *a*. The microscopical examination of the white contents of the necroses, which had the consistence of Neufchatel cheese, showed it to be composed of a mass of necrotic and oil-containing cells (compound granular corpuscles) and fatty-acid crystals.

PROTOCOL J. Similar experiment to I, except that the pancreas was not ligated. Dog killed on the seventh day. Several necroses near the pancreas. No tests.

PROTOCOL K. Dog; operation March 24th; veins tied, laceration of pancreas. Chloroformed March 26th. Numerous necroses in omentum, mesentery, and about pancreas. Tests positive from pancreas and necrosis (two situations); negative from fat at a distance.

PROTOCOL L. Cat; operation April 15th, 10 A.M. Ligation of veins; laceration of pancreas Chloroformed April 17th, 10 A.M. Peritoneum clean. Duodenal end of pancreas swollen and œdematous. The omentum shows several areas of hemorrhagic infiltration, with doubtful evidence of necrosis. What appears to be necrotic fat discovered along the sheaths of the portal vessels. Tests with pancreas, supposed necroses in omentum and fat at a distance certainly free; all failed to react excepting the first.

DISCUSSION.

DR. W. H. WELCH: Some years ago I brought before the Association a case of fat-necrosis of the pancreas in which the micro-organisms were present. This was the first demonstration on record of the finding of the colon bacillus in this organ, and I presented to the Association cultures of the colon bacillus taken from this situation. I remarked at the time that that organism had nothing to do with the necrosis—that it was only an accidental invader. That proved to be the case. In several other instances the same organism was found, but in some cases I must say it was most agreeable to have an explanation dissociated from the presence of micro-organisms.

ON THE APPEARANCE OF CERTAIN AMŒBOID BODIES IN THE BLOOD OF VACCINATED MONKEYS (RHŒSUS) AND CHILDREN, AND IN THE BLOOD OF VARIOLA.

An Experimental Study.

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SURGEON, U. S. A.

Even prior to the introduction of Koch's improved methods, Cohn had described his micrococcus vaccinæ. Chauveau and Sanderson had demonstrated that the active ingredient contained in vaccine lymph could be removed by filtration. The possibility of making use of solid culture media gave a new impulse to the search for the causative agent of vaccinia and variola, which has been assiduously continued since that time, as a rule, along the line of bacteriological research. Notwithstanding the many claims of positive results, these have in the end proven groundless, unless one excepts the latest claims of Klein[1] and Copeman[2] for the discovery, independently, in vaccine and variolous lymph of a short spore-bearing bacillus of peculiar staining properties and which refuses to grow on all of the usual media.

During the past ten years, and more especially during the last half decade, attention has been turned toward the possibility of the animal nature of the parasite of vaccinia and variola. Van Der Loeff,[3] in 1886, mentioned numerous small bodies capable of independent movement, which he discovered while examining the clear fresh lymph of a calf, as a hanging-drop in a warm chamber. He gives no other description of these bodies, which he assigned to the class rhizopoda. If the lymph had been taken with antiseptic precautions, these bodies were still to be found after months had passed; but if bacterial contamination of the lymph had occurred, they were

not to be seen after the lapse of one or two weeks. Impure lymph, in which these little bodies could not be found, was inactive; whereas the inoculation of pure lymph containing them was always followed by success, even at the end of several months. The following year the same observer[4] reported the presence of similar amœboid bodies, only more numerous, in lymph taken from two cases of smallpox at the commencement of the stage of pustulation.

Shortly after Van Der Loeff had published his observations, L. Pfeiffer[5] called attention to certain unicellular, round, or oval-shaped bodies constantly present in the lymph of vaccine and variola, which he believed to be parasites and assigned to the Sporozoa, Leuckhart, "Order monocystis." These parasites develop in the cells of the Malpighian layer of the skin, rapidly forming into cyst-like bodies. Propagation takes place by the formation of spores within the cyst-wall. The mature spore presents the appearance of a minute disk with vacuolation, out of which there appears to be developed an amœba-like embryo having independent movement. In 1888 Pfeiffer[6] found in human lymph numerous pale hyaline disks, without nucleus, which exhibited rapid, amœboid movements. Rieck,[7] confirmed Pfeiffer's finding in human, calf's, and variolous lymph. More recently (1895) Ogata[8] has made careful microscopic examinations of stained cover-slip preparations of fresh lymph. As a result of his studies, he finds in humanized, bovine, and variolous lymph certain protozoa which belong to the Class Gregarinida, Family Polycistidæ, Genus Clepsidrina, and is of the opinion that these are probably the causative agent of vaccinia and variola.

The first attempt to cultivate the supposed parasite of vaccine lymph was made by Guarnieri[9] in 1892. He first studied the changes which occur in the epithelial cells of the skin during the prepustular stage of smallpox. He always found certain small bodies half the size of the nucleus, or much smaller, which occupied the protoplasm of the affected epithelial cells and stained uniformly and regularly. The little bodies were of various shapes, most often roundish, with irregular margins.

Guarnieri next inoculated the cornea of guinea-pigs and rabbits with vaccine lymph, and obtained characteristic lesions, due to the development of a parasite within the deep epithelial cells of the cornea. At various periods of development—generally at the end

of forty-eight hours—scrapings from the cornea were made and examined while suspended in a hanging-drop of aqueous humor. Thus prepared Guarnieri always found within the epithelial cells of the affected area little shining, slowly moving amœboid bodies, which occupied the protoplasm of the cell, but did not obtrude upon the nucleus. Stained sections of the cornea, through the site of inoculation, examined under 500 diameters, showed that, while the superficial cells were not involved, almost every deep epithelial cell contained, beside its nucleus, a small deeply stained body which lay in the protoplasm and was surrounded by a narrow clear zone. Each cell, as a rule, contained one of these bodies, though two or more might be present in the same cell. Examined under one thousand diameters, these bodies were seen to consist of a round or oval nucleus, surrounded by a layer of protoplasm, which assumed various shapes. Guarnieri considers these bodies to be parasites, and assigns them to the protozoa. From the fact that the parasite occupies the protoplasm of the cell, which it destroys as it develops, Guarnieri designates it "citoryctes variolæ sue vaccinæ."

Ferroni and Massari,[10] in 1893, reported that after inoculation of the cornea of guinea-pigs and rabbits with croton oil and India ink, small bodies, like those described by Guarnieri, could be found in the epithelial cells, but in smaller numbers. They believe that the so-called parasites of Guarnieri are derived from the nucleus of the cells or from emigration of leucocytes.

In 1894 L. Pfeiffer[11] confirmed Guarnieri's experiments on the cornea of animals, and announced the discovery of the parasites, also, in the blood of smallpox patients, and in that of vaccinated children and calves, during the stage of fever. He described these parasites as amœboid cells one-half the size of a red-blood cell in the calf, and one-fourth that of a red-blood cell in the child. A nucleus is present which can be stained; sometimes the parasite contains two to four nuclei. They are provided with pseudopodia, and often with flagella, that can be stained with Lœffler's flagella stain. These bodies are not intracellular, but swim free in the blood. The movements of the parasites are different from those of the mononuclear and polynuclear leucocytes, and resemble closely those of amœbæ. According to Pfeiffer, there are two stages in the development of this parasite. The first consists of an infection of the

protoplasm of the epithelial cells by those bodies which were first cultivated in the corneal epithelium by Guarnieri. The amœbæ found during the stage of fever in the blood of vaccinated children and in smallpox blood belong, also, to this stage. Out of the young form occupying the epithelial cells develops the second stage, which presents itself as a kind of cyst—*monocystis epithelialis* of Pfeiffer—whose contents divide into a number of spores. The further development of the spore into the young form has not, as yet, been followed.

In the following year, 1895, Von Sicherer,[12] Clarke,[13] and E. Pfeiffer[14] published confirmatory observations of Guarnieri's experiments on the cornea. Von Sicherer pronounces the process to be a local infection of the corneal cells by a parasite, which, while destroying the protoplasm of the cell, leaves the nucleus undisturbed. E. Pfeiffer failed to find these bodies in the corneal epithelium of rabbits inoculated with chemical irritants, such as osmic acid, glycerine, croton oil, and lunar caustic; but they were uniformly present in the cornea of rabbits, goats, and calves inoculated with vaccine lymph. Pfeiffer also found in the blood of vaccinated calves amœboid bodies which continued their movements for several hours. His description is meagre, but his figure, No. 6, shows homogeneous amœboid bodies of various shapes, generally with one nucleus. These bodies approach in size a red-blood cell.

The foregoing embraces a brief review of the results obtained from a microscopical study of the local lesions of the skin in vaccinia and variola, and of the lesions of the cornea produced by inoculation with vaccine lymph. While not conclusive, the weight of testimony points strongly to the appearance within the corneal epithelium following local vaccination of certain definite bodies possessing independent amœboid movements, and which do not appear to be called forth by various chemical irritants.

As regards the claims of L. Pfeiffer that small, free-swimming nucleated amœboid cells appear in the blood of variola and vaccinia during the stage of fever, which bodies he considers as the much-sought parasite of these diseases, nothing confirmatory has so far been published.

At the suggestion of Surgeon-General Sternberg, I took up this line of investigation about one year ago, directing attention at first

to the microscopical examination of the blood of vaccinated monkeys and calves, and later to that of children and smallpox patients. The work was begun in April, and continued with slight interruptions until September, 1896. Except in the examination of the blood of smallpox patients, I was assisted by Dr. W. W. Gray, of the Army Medical Museum, and Dr. James Carroll, Assistant in the Laboratory of the Army Medical School, to the former of whom my thanks are also due for photomicrographs and drawings, and to the latter for daily valuable assistance in the blood-examination, covering a period of nearly five months.

The investigation was entirely confined to the study of fresh preparations of blood, which were examined with the greatest care; one at least of the observers making use of a mechanical stage for this purpose. During the earlier experiments the blood was examined only at the height of vaccination (seventh and eighth days). In the later experiments the period of examination was extended to cover the time from the day of vaccination to the subsidence of this process, and in several of the experiments the blood was examined during a number of days preceding and following vaccination.

The results obtained are believed to be of sufficient interest to warrant their report.

In all the vaccinations except one, glycerinated calf's vaccine was used. In the excepted case fresh monkey's vaccine was inoculated. The examination of the four animals—three monkeys and one calf—first experimented upon was entirely negative. The succeeding experiments gave more encouragement. The following are brief details of some of these:

Experiment V.—Monkey. Vaccinated May 5, 1896. Successful. Daily examinations of blood were made, beginning on the fourth day of vaccination. These were negative until the sixth day, when a body was found which attracted attention. It is in diameter about one-third that of a red blood-cell; its protoplasm consists of very fine granules, these being smaller than those of an ordinary neutrophilic cell. From the periphery of this small body clear, short, blunt bits of protoplasm are being continually projected and withdrawn. The granular portion of its protoplasm does not at any time flow into these clear pseudopodia, although the body changes its general shape, being sometimes round or oval or even triangular. At times a round or oval white spot resembling a nucleus appears in its granular protoplasm. It is kept under observation about six hours (cold stage), during which time its amœboid movements continue active, but the body does not change its posi-

tion. Other bodies of like granulation and size, some quiet, some amœboid, are observed. One of these bodies, seen on the eighth day and left in the field of the microscope during the night, shows at the end of twenty-three hours two distinct, long-curved processes resembling flagella Its amœboid movements have ceased, and its granular protoplasm appears darker and more condensed. On several occasions a neutrophilic leucocyte is seen to approach one of these bodies, envelop it completely, and then, after an interval of a few minutes, release the body and pass on. These small granular bodies are found by each of three observers on all slides examined on the seventh, eighth, ninth, tenth, and eleventh days after vaccination. (Plate I., Figs. 1–6.) Their number is not large, but as many as five can be found on one slide.

They cannot be found on the twelfth, thirteenth, and fourteenth days, although patient search is made.

Experiment VIII.—Calf. Vaccinated May 13, 1896. Successful. Examination of blood from first to eighth day. On the third day after vaccination there are seen a few finely granular bodies, one-fourth to one-half the diameter of a red cell, which are either quiet or slowly change their general shape, without projecting any clear protoplasm. Two similar bodies, however, are actively amœboid. These bodies continue to appear until the seventh day, when they can no longer be found. These small amœboid bodies, both as to appearance and character of movement, resemble closely those seen in Experiment V.

Experiment XI.—Monkey. Vaccination June 6, 1896. Successful. This animal's blood had been examined daily by two observers from May 22d to June 5th with negative results. There are seen, however, prior to vaccination, from time to time, small, roundish bodies, having a slightly greenish refraction and no distinctly granular protoplasm. These are about one-third the diameter of a red cell and possess amœboid movements. Small, short processes are projected which quickly assume the same greenish color as that of the body proper. They are not to be confounded with the granular bodies seen in vaccinia. After vaccination daily examinations are negative until June 12th, sixth day. On this day the granular, amœboid bodies appear in the blood in moderate numbers. They are in all respects similar to those described in Experiment V., except that some of them are smaller—scarcely so large as one-sixth the diameter of a red cell, and some have a slightly coarser and darker granulation. Distinct, clear, blunt processes are projected by these bodies, into which, as a rule, the granular protoplasm does not flow, though exceptionally this is seen to take place. Several of these granular bodies are still amœboid at the expiration of thirty hours. On the twelfth day a body unlike any heretofore seen in monkey's blood is found. It is one-half the diameter of a red cell, and consists of a number of fine, dark granules situated in the midst of a clear protoplasm. This body is rapidly amœboid, its clear periphery continually changing form and sometimes assuming rosette shapes. A few granular bodies are present on the fourteenth day. Examination on the fifteenth, sixteenth, and seventeenth days negative.

PLATE I.

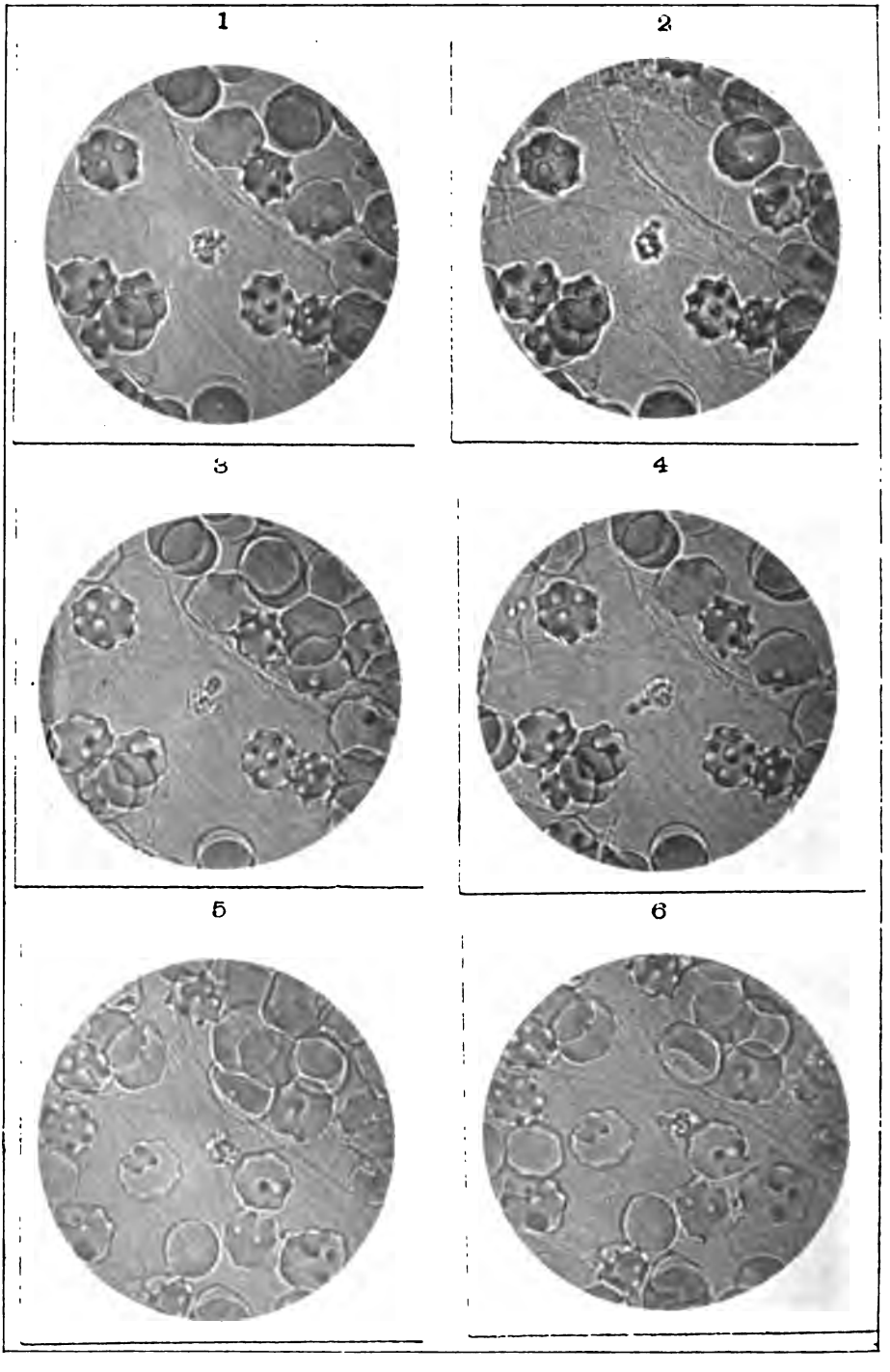
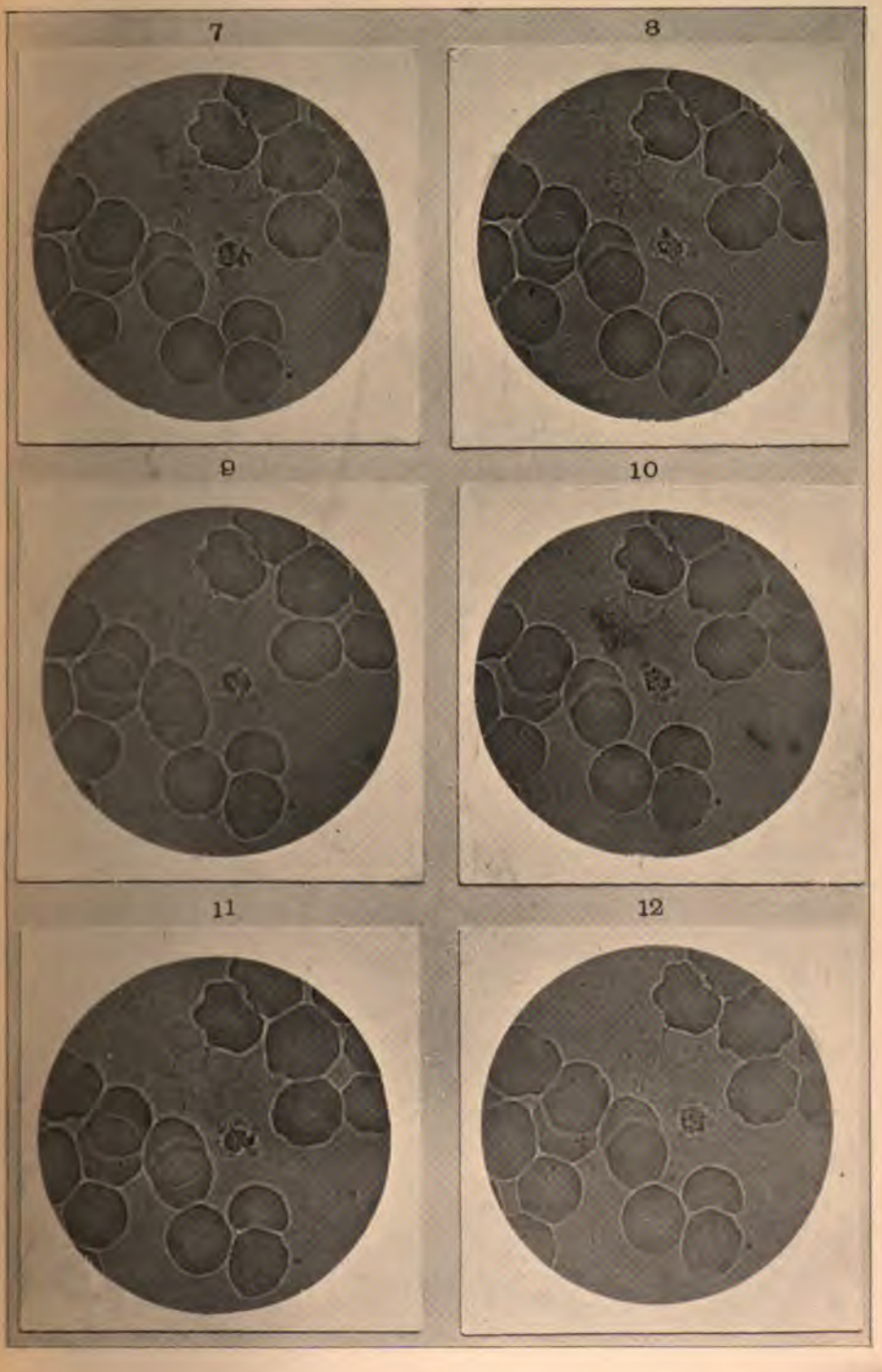


PLATE II.



Thus of eleven animals—nine monkeys and two calves—the blood of seven—six monkeys and one calf—contained during the stage of fever attending a successful vaccination certain extra-cellular small, granular amœboid bodies which did not correspond to any of the normal elements of human blood. A fact which appeared of additional interest was the discovery of quite similar amœboid bodies in my own blood five days after an accidental vaccination on the finger with fresh monkey's lymph. These bodies were present until the tenth day, but could not be found thereafter.

The time of appearance of the bodies in the blood of the vaccinated monkeys was as follows: fifth day, two; sixth day, four. There was observed, however, in the blood of one of the monkeys (Experiment 10) twenty hours after vaccination, an amœboid granular body similar to those which had been seen to appear toward the end of the first week of vaccination. No other bodies were found thereafter in this particular animal's blood until the sixth day. The bodies disappeared as follows: twelfth day, three; thirteenth day, one; fourteenth day, two. In the one positive experiment with the calf they appeared on the third day, and could not be found after the seventh day.

As these rather interesting bodies had been found in the blood of the seven animals last experimented upon, it was considered advisable to continue the investigation with vaccinated children. In this second series of experiments the blood of five children was examined—three white, and two black. The following are brief protocols of some of these:

Experiment XII.—Child, aged four years, white. Vaccination June 23, 1896. Successful. Examination of the blood on the day preceding vaccination is negative. Examination of blood taken thirty minutes after vaccination shows one small, faintly granular body, one-third the diameter of a red cell, which sends off clear, blunt processes after the manner of the bodies already described in the vaccinated monkey's blood. From this time until the seventh day examinations are negative. On this day there are observed a few pale amœboid bodies, one-half the diameter of a red blood-cell, containing a few fine, dark, dancing granules, which are slowly amœboid. Similar bodies are observed on the ninth day. Examination on tenth, eleventh, and twelfth days is negative.

Experiment XIV.—Child, aged two years, negro. Vaccination July 8, 1896. Successful. Blood subjected to daily examinations for one week preceding vaccination, with the result that, four days prior to vaccination,

there is found a finely granular, actively amœboid body, one-third the diameter of a red blood-cell, which sends off clear processes into which the granular protoplasm is not seen to flow. Twenty-four hours after vaccination a similar body is found. The results are then negative until the seventh day, when the small, granular amœboid bodies, as heretofore seen in monkey's blood, can be found in all fresh preparations. (Plate II., Figs 7–12.) Sometimes as many as nine of these bodies are found on one slide. There is also seen on the ninth day a pale, slightly refractive body, one-third the diameter of a red cell, which contains one coarse, dark granule centrally situated, while its clear periphery undergoes continual changes of shape. Examination of the blood on the fourteenth, fifteenth, and sixteenth day is negative. In this child's blood, prior to and during vaccination, the small amœboid body with slightly greenish refraction, which has been seen in the normal blood of the monkey, was found on several occasions.

Thus of the five children whose blood was carefully studied during the period of vaccination, three (two black and one white) gave a positive and two (both white) a negative result, as far as the finding of the small granular amœboid bodies was concerned. The case (Experiment XII.) in which the granular body was seen in the blood taken thirty minutes after vaccination but did not appear thereafter, is classed as negative. The bodies appeared in two cases on the sixth and in one on the seventh day; they disappeared from the blood in two cases on the fourteenth, and in one case on the seventeenth day.

When the latter experiments were about completed, the occurrence of an epidemic of smallpox on the island of Key West, Florida,* afforded the opportunity for the microscopic study of the blood of this disease. Unfortunately upon my arrival the epidemic had about spent itself, so that only three cases could be examined, with the following result:

Observation XVII.—White boy, aged eleven years. Discrete smallpox. Seventh day of eruption. The same granular bodies, both as to size and amœboid movements, as seen in the blood of vaccinated monkeys and children, are found. In addition, there are observed on each slide pale, amœboid bodies, few in number, which contain a few fine or sometimes coarse, refractive, pigment-like granules. The size of these pale bodies is about one-half that of an ordinary red blood-cell. They are generally actively amœboid, continually changing their outline and sometimes assuming rosette-shaped forms. These amœboid bodies are present on the eighth day. One of these

*Through the courtesy of Dr. J. Y. Porter, State Health Officer, and Dr. Joseph H. White, Passed Assistant Surgeon, U. S. Marine-Hospital Service, officer in charge of the Smallpox Hospital, Key West, Florida, every facility was afforded the writer in conducting this investigation.

is kept under observation for several hours. Its granules, few in number, remain centrally situated, while its periphery is rapidly changing, clear processes being quickly projected and withdrawn. It is left in the field of the microscope during the night, and fifteen hours later presents the appearance of a quiet round body, one-half the diameter of a red cell, with a pale, refractive peripheral zone and a granular centre, the latter made up of a number of quite dark, refractive granules.

Examination of the blood on the ninth day is negative.

Observation XVIII.—Negro, aged eleven years. Discrete smallpox. Fourth day of eruption. The granular, amœboid bodies and the pale, amœboid bodies, such as have been described in the preceding observation, are found daily from the fourth until the seventh day of the eruption. No examination made on the eighth day. On ninth and tenth days the examination is negative.

Observation XIX.—Negro, aged seventy years. Confluent smallpox. Eighth day of eruption. No granular, amœboid bodies are seen in this blood. Pale, amœba-like bodies are observed. These vary in diameter from one-third to one-half that of a red cell. Kept under observation for a considerable time, they show frequent changes of shape and contain a few fine, dark, dancing granules. One body particularly arrests attention. It contains within its pale protoplasm a few very fine, pigment-like granules—eight at most can be counted—which are, as a rule, gathered to the centre, though they may be, at times, scattered. This body is very active in its movements, remarkably large, blunt pseudopodia being rapidly sent forth in various directions; as many as four at one time. Two hours later it has assumed the form of an oval amœba, one-half the size of a red cell, and changes its general shape very slowly. The dark granules are no longer gathered to the centre, but are distributed throughout the body. This patient died the same day, so that further examination could not be made.

Thus of three cases of variola, the small granular amœboid bodies were present in the blood of two, and absent in that of one (blood examined on the eighth day of eruption only). Paler amœboid bodies were found in the blood of three, their appearance in one case being as early as the fourth day of eruption. In two cases they were found on the seventh and eighth day of eruption, respectively. In two cases they were not found on the ninth day.

In view of the results obtained from a study of the blood of variola it was considered advisable to study the blood of variolated monkeys. Hence, soon after my return, the following experiment was made:

Experiment XX.—Monkey. Variolated August 8, 1896, with fresh lymph taken from a discrete case of smallpox, seventh day of eruption. Successful.

This animal's blood has not been examined prior to inoculation. First day's examination is negative. On the third day after vaccination small, finely granular, amœboid bodies are observed. These are seen on the fourth, fifth, and sixth days. There are also found on the fifth and sixth days a few pale, amœboid bodies, in size one-half the diameter of a red cell. These exhibit active movements and contain a few dark, pigment-like granules. They resemble the pale amœboid bodies seen in the blood of variola. Examination on the seventh, eighth, and ninth days is negative.

In view of Pfeiffer's statement, that small amœboid cells are to be seen during the stage of the fever in the blood of vaccinated children and calves, the discovery in the blood of vaccinated monkeys, also, during the stage of fever, of granular, amœboid bodies much smaller relatively than any of the white elements heretofore described in normal human blood, naturally aroused much interest as to their true character. Their disappearance, too, about the end of the second week, did not lessen the important and intimate relation which these bodies appeared to bear to the local inflammation. Their minute size, their active amœboid movements, the persistency of the latter, together with the occasional phenomenon of phagocytosis, all seemed to point to the parasitic nature of these bodies as claimed by Pfeiffer.

The discovery, however, of a similar body in the blood of a monkey within twenty-four hours after vaccination, and in the blood of a child thirty minutes after vaccination, necessarily raised a doubt as to their causative importance. It seemed possible, after all, that such bodies might be occasionally found in normal blood, and that during vaccination they might appear in larger numbers in the general circulation. This led to a thorough search for these diminutive bodies in the normal blood of monkeys and children. As a result of this search, there was found in the blood of one monkey and of one negro child, prior to vaccination, a body having the same appearance and size as those seen in the blood of vaccinated animals. The failure to observe this small granular body heretofore in normal blood must be attributed to its extreme scarcity and relatively small size. The tendency, too, to overlook such small bits of protoplasm would be natural, since on casual inspection they might readily be mistaken for parts of a fragmented leucocyte.

The origin of these small granular bodies, rarely seen in normal blood, as well as their possible identity with those bodies observed by Pfeiffer and myself in the blood of vaccinated animals and chil-

dren, and in that of smallpox, must be left to future observation to determine. Their appearance in the general circulation in vaccinia about the end of the first week, in such numbers that a few may be found in every well-made preparation of blood, and their prompt disappearance about the end of the second week, are indicative of their importance, whatever may be their real significance.

The pale, amœboid bodies which were observed in the blood of three cases of smallpox and of one variolated monkey, will, it is hoped, attract the attention of other investigators. Bodies such as these have not been found during this investigation in the normal blood of animals or children.

Conclusions.

1. The claim of L. Pfeiffer, that small granular amœboid bodies are present in the blood of vaccinated children and calves, and in the blood of variola during the stage of fever, is confirmed. A nucleus has not been positively made out in any of these bodies.

2. Granular amœboid bodies, about one-third the diameter of a red-blood cell, appear, also, in the blood of the monkey during the active stage of vaccinia, and disappear with the decline of the local inflammation.

3. A body of like appearance, granulation, and size may occasionally be found in the normal blood of monkeys and children.

4. Pale amœboid bodies, containing a few dark pigment-like granules, are present in the blood of variola and in the blood of the variolated monkey. Bodies of like appearance may occasionally be found in the blood of vaccinated children and monkeys.

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TWO CASES OF ERYTHROMELALGIA (MITCHELL).

By D. W. PRENTISS, M.D.,
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CASE I. *Female, aged fifty-eight years; left hand only affected.*—Mrs. C., aged fifty-eight years; neurotic diathesis, but has kept up and worked hard in household duties, keeping a summer hotel. Before this attack was "run down" physically. Disease first began in August, 1895, with burning pain in first finger of left hand at angle of nail next the thumb, and continued for two weeks in the first finger. In the autumn of 1896 extended to second and third fingers, then to the fourth, and finally to the thumb.

A large, tender swelling developed at the base of the thumb, and this winter there is another tender spot on the back of the hand, over the third and fourth metacarpal bones. Sometimes over the abductor minimi digiti muscle. The pain is of a severe, burning character, lasting sometimes for days together, with remission, but not entirely absent during the attack

The ulnar artery was cut at the wrist several years ago by a broken lamp-chimney, and was tied. The patient thought, perhaps, the nerve was injured, and this caused the trouble. This is hardly likely, however, as the pain began and has been most severe in the radial side. Stimulating the ulnar nerve at the elbow causes twitching of the third and fourth fingers.

The character of the pain during an exacerbation is of a severe, burning nature, and paroxysmal, but the parts are always tender until the attacks pass off, then there will be freedom from pain until the next attack. Previous treatment consisted of local applications, as chloroform, tincture of iodine, blistering, etc., and general treatment in the form of tonics, and especially for dyspepsia.

Paroxysms of pain were in recurring attacks from three to six weeks apart. Pain was better on lying down. Had typhoid fever thirty years ago. No history of malaria or of specific disease.

October 31, 1896. She came under my care, suffering from the symptoms just stated. The pain was evidently very severe, as shown by the facies. It was felt most severely in the thumb and first and second fingers of the left hand, which were of a purplish-red hue and swollen. The worst pain was in the ball of the thumb, which was swollen and very tender. The general health was impaired. Heart's action weak, but otherwise normal. She was

very nervous and slept badly on account of the pain. There was also pain up the arm to the back of the neck—described as a drawing pain, extending also to the ears, jaws, and throat, with a dull ache of the head and blurring before the eyes.

No dizziness, but occasional difficulty in walking (ataxia). Knee-jerk normal.

Dyspeptic symptoms very marked, and aside from the pain in the hand it was the dyspepsia which called especially for treatment.

The character of the indigestion is that common in neurasthenia—from innervation—not from organic stomach disease.

For relief of pain:

℞.—Phenacetin 2.00
Caffeine 1.00

M.—Ten capsules. S.—Two every hour until relieved or until six are taken.

Usually one dose gave partial relief.

She was given nitroglycerin, one and one-half milligramme, three times a day, with tonics and bismuth and carefully regulated diet. After two weeks of the treatment without benefit, galvanism was applied from the hand to the back of the neck daily—three minutes at a time. This was continued with the nitroglycerin and tonics for a month, without apparent relief, the daily pain still continuing. It was then stopped for awhile, but the pain became worse, and galvanism was again resorted to. The relief, however, was nothing to boast of, though it appeared to be the treatment that offered the best hope of good result.

The nitroglycerin to strengthen the action of the weak heart and stimulate freer passage of blood through the capillary system, by dilating arterioles, also electricity, the constant current, with positive pole in the hand and the negative at the back of the neck, should relieve pain in the hand and relax spasm.

The treatment here outlined was carried out for three months with little or no relief. The patient improved somewhat in general health, but there was no improvement of the pain in the hand. It fluctuated—sometimes better, sometimes worse—until

February 18th, when the most violent attack of all occurred, the pain being of an intense, burning character, extending to the whole hand, though more severe at the points previously indicated, and following up the arm to the shoulder.

The color was purplish-red with œdematous swelling of the parts most affected. The last joint of the middle finger was livid, as from strangulation, and appeared as though gangrene might follow.

During the previous night she had taken six capsules of phenacetin and caffeine (of the former 1.20 grammes in all) without relief of pain, but with profuse sweating.

A prescription containing extract of cannabis indica, 0.03; extract of

FIG. 1.

Palm of hand during a paroxysm; Feb. 18, areas of pain shown by the shading.

FIG. 2.

Back of hand during a paroxysm ; Feb. 18, areas of pain shown by the shading.

belladonna, 0.01, and salicylate of cinchonidia, 0.20 to the dose, to be taken every three hours, was ordered, and at night hypodermic.

Holding up the hands gives relief.

A hypodermic injection of morphia and atropia was given, which later secured relief and a good night's rest.

FIG. 3.

Palm of hand showing character of the swelling.

Pain returned with less severity the following day.

The hypodermic was repeated in a smaller dose the next night, with the same good effect, and then no longer needed.

CASE II. *Female, aged thirty-seven years. Disease in both feet.*—Mrs. A., widow, aged thirty-seven years, a neurasthenic, with severe dyspeptic symptoms. No constitutional taint, as far as known; no history of malaria. Pain in the heels began three or four years ago, and has recurred at intervals of three or four months, the attacks lasting from two to three weeks. During the interval is comparatively free from pain.

The paroxysms seem to be brought on by physical exhaustion or any kind of strain to the nervous system, especially if obliged to stand or walk more than usual, as on one occasion when called to nurse her mother in a prolonged illness.

The pain begins as a dull ache with burning sensation; at first with a sensation of pebbles under the heels. As the attack progresses the burning increases and extends to the sole of the feet and up the calves of the legs.

When pain becomes severe the heels are red and swollen, and shoes cannot

be worn, as the attack increases in severity. A peculiar sensation extends to the head, restlessness and hysterical symptoms, and a disposition to scream. When asked as to severity of pain, said it was so bad that she felt "she just could not stand it another moment."

Lying down relieves, except when at the worst, then the restlessness forced her out of bed, and rubbing would give her temporary relief. Cold relieves. Putting the feet out from under the cover was grateful. At my suggestion cold water was tried with benefit. Attacks more frequent and worse in summer than in winter and also when feet get warm in bed.

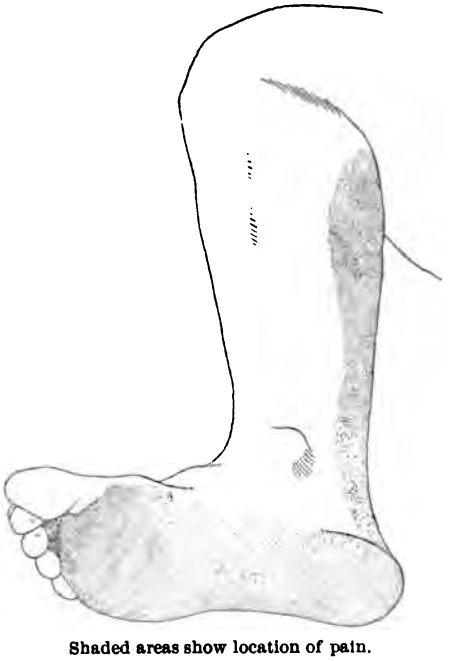
She is drowsy and dizzy much of the time, and frequently shows an ataxic gait.

Treatment has been directed to the general condition—the dyspepsia and neurasthenic symptoms.

She has an idiosyncrasy against strychnia, the latter causing dizziness and vertigo.

No disease of special organs discoverable.

FIG. 4.



Shaded areas show location of pain.

This disease is undoubtedly a rare one, and fortunately so, for, as Dr. Mitchell says, treatment is almost unavailing, though patients

often go on for years without becoming worse. It occurs almost always in the feet. Out of sixteen cases reported by Dr. Weir Mitchell (*American Journal of the Medical Sciences*, 1878, vol. lxxvi.) only one was in the hands alone, and in two the hands and feet were both affected. All of the others were in the feet. He gives as the characteristic symptoms redness, intense burning pain, and at the beginning rise of temperature, but later fall of temperature, with probably inflammation of nerves affected. It usually commences in the ball of the foot, or the heel, or the great toe, and extends to the sole and dorsum. The disease is more common in men than in women—twelve out of the sixteen cases reported by Dr. Mitchell were men.

Another peculiarity of this affection is that it is aggravated by heat and relieved by cold. In Dr. Mitchell's cases relief came from lying down, although in a case treated by prolonged rest—while the patient was perfectly comfortable in bed—the pain returned in full force on getting up and walking.

In the first case cold does not relieve the pain, and but little relief accompanies the recumbent posture, probably because it is in the hands instead of the feet.

The causes of the disease are obscure. It seems to follow a depressed state of the nervous system, neglected neurasthenia, long standing on the feet, long marches, as of soldiers; reflex irritation, especially of the male urethra. But the disease is so rare and these causes so common that such reference is unsatisfactory.

As to treatment, it is equally unsatisfactory. The indications are to relieve symptoms and improve the general health.

Neurotic or neurasthenic symptoms by baths, spinal douches, good food and air and tonics. The dyspepsia should receive attention.

For the relief of pain, cold applications. These cases are, as a rule, made worse by heat and relieved by cold. They are worse in summer and better in winter, so that a cool summer climate is indicated.

Galvanism—the positive electrode at the periphery; the negative to back of neck.

Rest in bed, where pain is very severe.

Possible surgical operation where indications are found. In the

present case I think stretching or cutting of the nerves of the forearm should be tried if the pain continues.

In regard to medicine to relieve the pain, Case I. has had phenacetin and caffeine with good effect. Cannabis indica and belladonna proved unavailing.

From the chronic character of the pain opium and its preparations should be avoided if possible. But sometimes the suffering is of such an intense character that morphia is imperatively called for, preferably under the skin in combination with atropia.

As to diagnosis in erythromelalgia, according to Dr. Mitchell, there is no other disease or group of symptoms in a well-marked case with which it can be confounded. There are many painful affections of the feet and hands, such as the effects of gout, rheumatism, sprain from flat-foot, nodes from syphilis, etc.; but none in which the train of symptoms found here exist. And that the disease is rare is evident from the comparatively few cases reported, although Dr. Mitchell predicts that attention having been called to this form of nerve disease it will be found more common than previously supposed. The pathology of these cases is involved in doubt. Erythromelalgia is classed among the vasomotor diseases, such as angio-neurotic œdema and Raynaud's disease. The pain either precedes or is simultaneous with the redness and swelling. In the case of Mrs. C. they came on at the same time. In the second case pain preceded the redness. This would seem to indicate that the sensory fibres of the nerves were first affected, the vasomotor becoming involved secondarily as a result. This is also borne out by the severe pain on pressure at the points most affected. With the redness and swelling, however, the pain is greatly aggravated.

The diseases to which it is most nearly allied are angio-neurotic œdema and Raynaud's disease.

In the former there are three forms described. The pale form (neuro-lymphangioma), due to dilatation of the lymphatics of paretic origin; the red form, due to angio-paralysis, and the dark-red, purplish form, caused, according to Eskridge (Wilson's *Applied Therapeutics*, p. 981) by spasm of the arterioles, which "checks the *vis a tergo* of the arterial current in propelling the current forward, and spasm of the small veins, which may force the blood backward into the arterioles."

Some such explanation as this may apply to erythromelalgia, but is altogether hypothetical.

Angio-neurotic œdema is supposed to be a form of urticaria—"the greater urticaria"—a functional nervous disease, caused by indigestion or transient nervous excitement. In some of the cases which I have seen it has been attributed to a spider bite—I need not say without cause. The element of pain is secondary in angio-neurotic œdema, and not important.

This disease cannot be confounded with the one under consideration.

The diagnosis for Raynaud's disease, though still more marked, deserves special notice, since many of the cases of erythromelalgia reported by Mitchell were pronounced by high authority to be cases of Raynaud's disease (Osler's *Practice of Medicine*, 1892, p. 962). The two diseases in many respects are the opposite of each other. This is perhaps best shown in the comparison in parallel columns given by Lannois (article on "Erythromelalgia," 1880, p. 71; Weir Mitchell's *Clinical Lessons on Nervous Diseases*, 1897, p. 179).

Local asphyxia (Raynaud).	*Erythomelalgia* (Mitchell).
Sex, four-fifths females.	In twenty-seven cases two were females.
Begins with ischæmia.	Little or no difference in color until foot hangs down in upright posture, when it becomes rose-red.
Affected part becomes bloodless and white. In certain cases there is the deep, dusky congestion of a cyanosed part, with or without gangrene.	Arteries throb and parts become of a dusky red or violaceous in tint.
Pain may be absent or acute, and comes and goes; has no relation to position; may precede local asphyxia.	Pain usually present; worse when part hangs down or is pressed upon. In bad cases more or less at all times.
Unaffected by seasons. In many cases all the symptoms can be brought on by cold.	Worse in summer and from heat; eased by cold.
Anæsthesia to touch.	Sensation of all kinds preserved.
Analgesia.	Hyperalgesia.
Temperature much lowered and unaltered by posture.	Temperature greatly above normal; dependency causes, in some cases, increase of heat; in others lowering of temperature.
Gangrene local and limited; likely to be symmetrical.	No gangrene; asymmetrical.

This comparative statement should make it clear that erythromelalgia and Raynaud's disease are distinctly separate.

Two other conditions are mentioned as belonging to diseases of the vasomotor system, namely, adiposis dolorosa (Dercum's disease)

and acromegaly, both attended with peculiar changes of nutrition and without doubt from disease of the central nervous system.

In acromegaly there was found "enlarged pituitary body, with enlarged sella turcica, persistence of the thymus gland, and hypertrophy of the fibres and glands of the vasomtor system (Wilson: *American Text-book of Applied Therapeutics*, 1896, p. 988). These facts are mentioned as having a bearing upon the plausibility of erythromelalgia being essentially a central disease.

There is more reason for this hypothesis in the fact that a number of the cases reported developed into well-marked disease of the cerebro-spinal axis and ran their course to a fatal result (Mitchell). Dr. Mitchell was disposed at first to this opinion, but in his recent work (*Clinical Notes*, 1897, p. 180) he "inclines rather to some of that new clinical perplexity, peripheral neuritis."

The action of ergot (ergotism) in producing gangrene of the extremities is of interest as bearing upon the general question of causation of vasomotor affections by central disease.

Ergot acts upon the vasomotor centres—in small doses by stimulating, in large doses by depressing (H. C. Wood's *Therapeutics*). Dr. H. C. Wood mentions a case (*loc. cit.*) of fatal ergot-poisoning in which there were gastric irritation, thirst, diarrhœa, *burning pain* in the feet, and convulsions.

The principal vasomotor centre is in the medulla oblongata, between the corpora quadrigemina and calamus scriptorum (Ludwig and Thiry, Owsjannkow; and Dittmar, Erb-Dis. Medulla Oblong.). Also in spinal cord, secondary centres in gray matter as far down as the lumbar vertebra (Goltz, Vulpian, *loc. cit.*).

Dr. Schenk, in an article published recently in the *Medicinische Presse*, states the disease is no doubt due to vasomotor disturbance consequent on an ascending degeneration in the posterior column of the cord. Woodnut has also described a case of erythromelalgia, attributing it to myelitis (London *Lancet*).

Referring again to Mitchell's *Clinical Notes*, he says:

"At the time I wrote (1878) I should, if driven to be positive in statement, have inclined toward considering this malady as due to some form of spinal disorder.

"But at present the reasonable explanations incline rather toward some form of that new clinical perplexity—peripheral neuritis." (*Loc. cit.*, p. 180.)

In Case LVIII. (of *Clinical Lessons*, not the fifty-eighth case of erythromelalgia) the disease was the result of an injury—a stone falling on the foot.

This case is reported in great detail, and serves to strengthen the theory of peripheral neuritis, from the fact that it was caused by (or followed) a local injury. Dr. Mitchell further goes on to say:

"I use the word neuritis, nerve-end neuritis, with more or less doubt. Some such distinct affection of the smaller nerves does seem to me probable, but whether it is congestion, neuritis, or some other of the undescribed changes in the lesser nerves or in the ultimate nerve-plates, we may not as yet decide with certainty."

Again (*loc. cit.*), "Neuritis is becoming a sad puzzle. We may have it with paresis and little pain; we may have it without notable paresis and horrible pain. It exists with or without notable myositis."

Again, "It may give rise to causalgia, joint-troubles, and alterations of nails and hair. It may fail to disturb nutrition, or greatly to alter local heat. And, lastly, if erythromelalgia be a neuritis it may cause pain and flushing, and to these increased enormously by dependency of the part may add such a rise of temperature as is rarely seen in acute local inflammation."

Dr. Mitchell continues to discuss the possibility of the existence of neuritis of such a character as to single out individual elements in a nerve containing fibres of sensation, motion, nutrition, and vasal control—affecting some and not others. Such an hypothesis seems untenable.

In Case LVIII., previously referred to, the excised portions of the musculo-cutaneous and internal saphenous nerves were examined microscopically and found "absolutely normal."

To sum up the pathology of them, we have the choice between:

1. Disease of the central nervous system, or

2. Peripheral neuritis affecting principally or only the smaller nerves or nerve-endings.

In the former we should expect the disease to be located in the medulla oblongata between the corpora quadrigemina and calamus scriptorum, or in the posterior segment of the spinal cord as far down as the lumbar vertebræ.

The central theory seems the more plausible, but at this time is purely hypothetical, there being no dissections to support it.

The opinion of peripheral neuritis of a peculiar character is given

a show of plausibility from two cases reported by Dr. Mitchell which followed local injury.

However, in both of these cases operated on, the nerves were exsected, and the nerve-trunks thus removed found normal.

This fact would locate the neuritis in the nerve extremities.

We will close this report by a reference to treatment, which, unfortunately, can be shortly disposed of. Thus far curative treatment has been of no avail, except in one case, by surgical interference.

The treatment divides itself into three indications:

1. That of the general health—neurasthenia, nervous dyspepsia, and hysteria especially.

2. The relief of pain. For this purpose phenacetin protected by caffein seems of first value. Cannabis indica and belladonna in the first of the present cases proved useless, as did also the phenacetin in the most violent paroxysms.

During the latter subcutaneous injection of morphia is imperative, but the objection to its frequent use is obvious. Rest in bed and cold applications have their place. Wendel reports a case cured by liq. acidi arseniosi, together with general treatment (*New York Medical Record*, 1890, vol. xxxviii. p. 545).

3. Surgical treatment. Exsection or stretching of the nerves was contemplated in the first case, but there being no precedent for it, and fearing serious nutritive changes, it was not determined on. This was before reading Dr. Mitchell's *Clinical Lessons*, 1897, in which he reports two cases thus treated, the first one with success in relieving the patient. In the second case, however, gangrene, resulting fatally, followed.

The operation in the former cases, the first of its kind in this disease, I quote from Dr. Mitchell's book (*loc. cit.*, p. 192):

"Dr. Keen operated on April 10th. He exsected two and a half inches of the muscular cutaneous nerve and the same length of two branches of the internal saphenous. The two end branches (plantar) of the posterior tibial nerve were stretched at the internal malleolus with a traction of fifteen pounds thrice used. The result next day was remarkable. There was almost immediate relief. The foot could be squeezed, pinched, or pricked without pain. Anæsthesia was not as extensive as we were led to expect it might be. The day following the operation the temperature—right, 95°; left, 93.5°; mouth, 99.5° (it was the right foot operated). On the right clonus still present, and knee-jerk was still extensive. The wound healed in a

few days. On May 4th the patient was able to walk on crutches. Clonus had disappeared and reflexes were no longer exaggerated. There was still some flushing when pendant, but no pain nor hyperæsthesia. When discharged—May 6th—he could walk well, but was ordered to continue the use of crutches as a measure of precaution, and had also a bandage applied daily.

"Dr. Kyle reports culture of blood and nerves obtained at the operation as yielding purely negative results. . . . June 7th, S. is reported well, and walking easily without crutches. Six months later he was at his work, as a stonemason, and entirely free from pain."

Thus it appears that at least one was cured by surgical procedure. The second case thus treated (Case LIX. of *Clinical Lessons*) was more unfortunate. I will only mention the operation and result.

Operation April 12, 1894, by Dr. T. P. Morton. Four inches of the musculo-cutaneous nerve and five inches of the internal saphenous excised. The posterior tibial behind the internal malleolus stretched with force of twenty-eight pounds. On the fifth day gangrene developed. A week later amputation was performed, with death on the operating-table.

Commenting on this case, Dr. Mitchell says: "As to operative relief I think that in future I should stretch all the nerves and leave the section of their trunks to be resorted to if milder means gave no fortunate results" (*loc. cit.*, p. 204).

In conclusion I append titles of bibliography of erythromelalgia, taken from the card catalogue of the Library of the Surgeon-General's Office. These titles do not appear in the large published *Index Catalogue*.

The disease had not been differentiated at the time the volume of the *Index Catalogue*, in which they would have appeared, was compiled.

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THE ROENTGEN RAYS IN THORACIC DISEASES.

By FRANCIS H. WILLIAMS, M.D.,
OF BOSTON.

ABOUT a year ago I had the pleasure of presenting to this Association a paper in which I related some of the early steps in my study[1] of the adaptation of the X-rays to medical practice; X-ray examinations were then a novelty, but they must now be accepted as a valuable supplement to our other methods of examination. To-day I wish to outline some of the results of the work of the past year, during which I have examined by means of the X-rays more than five hundred patients—about one hundred of which were surgical cases—at the Boston City Hospital and at my office.[2] The majority of the four hundred medical cases were suffering from some thoracic disease. Certain of these patients—those ill with pneumonia, for instance—have been examined a number of times, as I wished to watch the progress of the disease and see the conditions presented in its different stages.

No harmful effects have been received in any way by these patients, and there need not be the slightest anxiety on the part of any one if proper precautions are taken. I have seen, however, several per-

[1] During the progress of this study I have reported my results at medical meetings or by published articles, as follows:

Meeting of the Suffolk District Medical Society, April, 1896.

Meeting of the Association of American Physicians, April 30, 1896. "Notes on X-rays in Medicine."

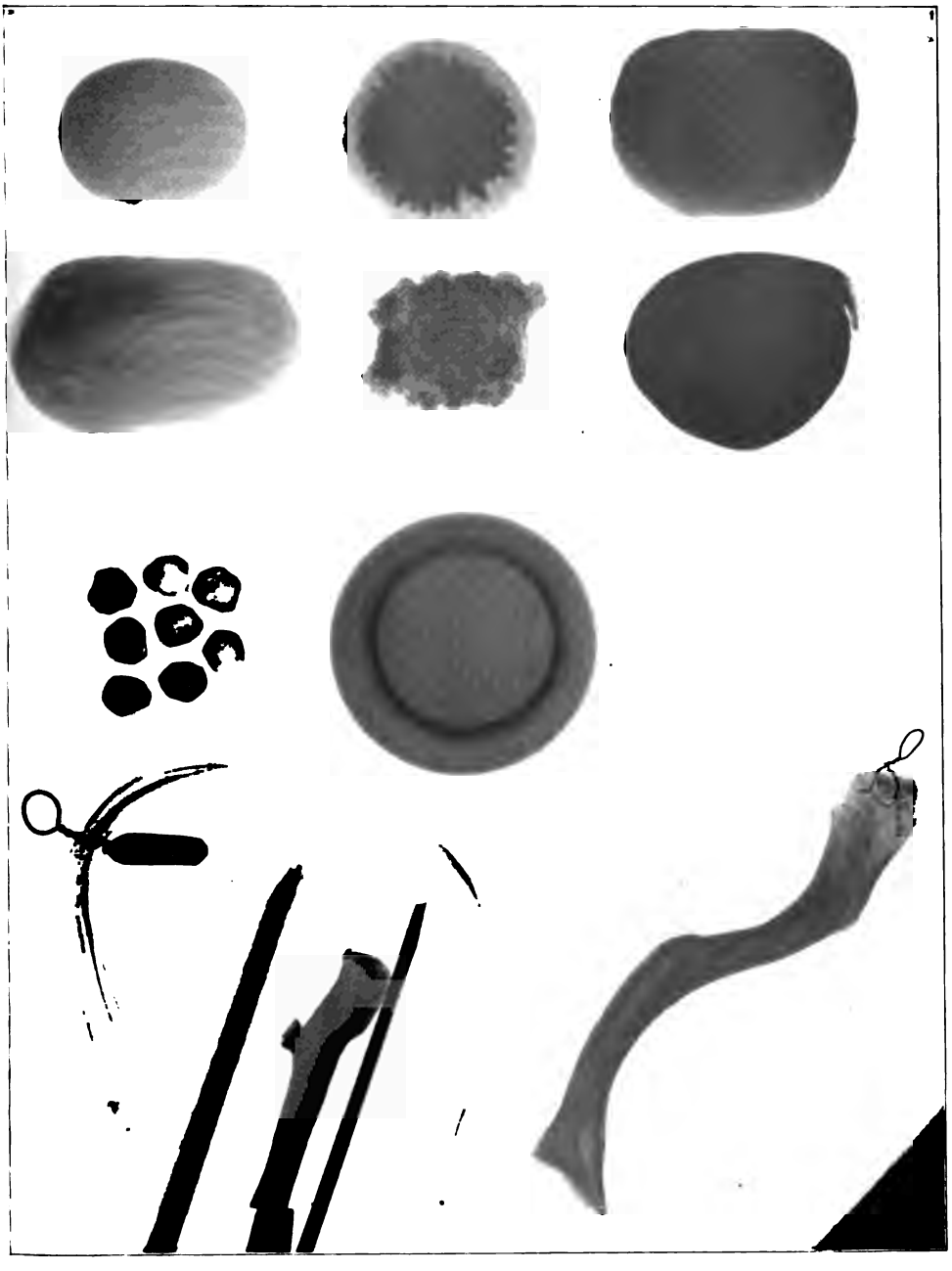
Proceedings of the Association of American Physicians, 1896. Boston Medical and Surgical Journal, October 1, 1896. "A Method for more fully Determining the Outline of the Heart by Means of the Fluorescope, together with other Uses of this Instrument in Medicine."

Meetings of the Boston Society for Medical Improvement, and of The Medical Society of the Boston City Hospital, October and November, 1896.

Medical and Surgical Reports of the Boston City Hospital, January, 1897, pp. 134-190. "A Study of the Adaptation of the X-rays to Medical Practice."

[2] In making these examinations I have used a Wimshurst machine and an induction coil, but principally the former, both of which were designed by Messrs. C. L. Norton and R. R. Lawrence, of the Massachusetts Institute of Technology.

PLATE I.



The two upper rows of objects in this radiograph are calculi. The two calculi on the left are composed of uric acid and urates; those on the right of phosphates; and the two in the middle of oxalate of calcium and uric acid, the upper one of these last two having an outside coating of urates. In the centre of the picture is a round aluminum cup, containing water, one inch in depth, and on either side of this cup is a group of gallstones, and to the right and below the cup a single large gallstone is seen indistinctly. In the left-hand lower corner is a decalcified bone, bent into the shape of an inverted u, with a lead tag attached by a copper wire. The decalcified bone surrounds an incinerated bone, which is lying on a piece of cotton-wool in a wooden box with a glass side. In the right-hand lower corner is a dry bone; in the extreme right-hand corner is a triangular piece of lead. The picture is reduced to one-half of its original size.

sons who have suffered a more or less severe inflammation of the skin, the nails also being sometimes involved, but they were all individuals whose occupation brought their hands into close proximity to the Crookes tube, or who, for purposes of testing its possibilities for harm, had exposed some part of the body to its action at a distance of a few inches for a considerable period; but there are simple ways of obviating these effects.

The varying resistance which the different tissues of the body offer to the passage of the X-rays depends upon difference in bulk and in chemical composition; organic substances made up of carbon, hydrogen, and nitrogen, which have a low atomic weight, allow the rays to pass readily, while those like bone, containing calcium, which has a comparatively high atomic weight, offer more resistance to the rays. The soft tissues of the body contain a large percentage of water, and most of them offer about the same resistance as an equal thickness of water. The various fluids found in the body in health and disease, such as the blood, ascitic and pleuritic fluid, pus, urine, fluid from hydrocele, etc., offer about the same resistance as water.

The following experiment with calculi (see Plate I.) illustrates in a striking manner how important to us is a knowledge of the chemical composition in our use of the Roentgen rays in medicine. Before attempting to detect any form of calculi in the body I first placed several different kinds over a photographic plate, which was enclosed in dark paper to shield it from the light, and exposed them for a few minutes to the X-rays. The rays penetrated the calculi made up of uric acid, of cholesterin and biliary salts very readily, but were obstructed by calculi containing oxalate of calcium in considerable proportion, phosphate of calcium, or other inorganic constituents.

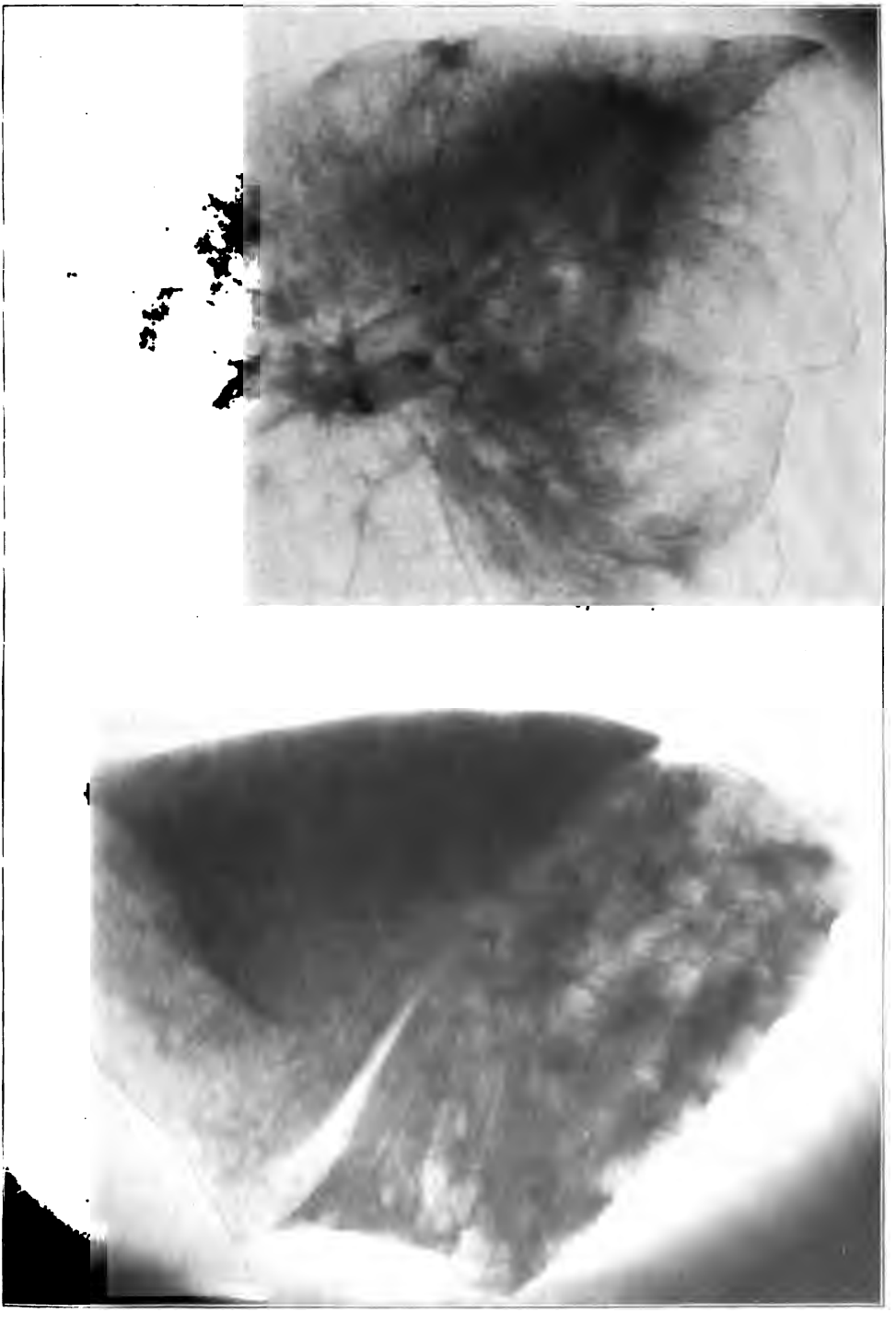
There is one other point which must not be overlooked in this connection, and that is the difference in resistance which air and water offer to the passage of the X-rays. The rays pass through air much more readily than through water, and as air makes up a certain bulk of the body a large part of the chest is filled with it, while water enters into the composition of all parts of the body and forms the chief constituent of the soft parts, it is readily seen of how much importance is this difference in permeability of air and water by the rays on account of the great contrast which is thereby afforded

in health between the lungs and their adjacent tissues or organs. Further, as will be shown later, one of the best opportunities for the advantageous application of the X-rays is obtained from the contrast of the normal lung tissue with that offered by pathological conditions which occur in the thorax, involving chiefly increase in density in the lungs or in the space usually occupied by them.

To use the Roentgen rays successfully in practice it is first essential that the physician become familiar with the appearances in the fluorescope which present themselves in health. This applies particularly to the thorax, and the picture of this part of the body, when seen in the screen of a large fluorescope, presents so much that it should be studied systematically. The trunk appears lighter above than below the diaphragm, and the rise and fall of this muscle, which is dark in the fluorescope, are distinctly seen. The chest is divided vertically by an ill-defined dark band [this band varies in width and definition according to the intensity of the light], which includes the backbone, on each side of which the lungs, forming the brightest part of the picture, are crossed by the darker ribs. The pulsating heart is seen, especially the dark ventricles, a portion of the venæ cavæ, and, under favorable conditions, the lighter right auricle and a part of the pulmonary artery. A small portion of one side of the arch of the aorta may be observed in the first intercostal space to the left of the sternum. After this general view has been taken the outline of the lungs should be noted during full inspiration and expiration, and the excursion made by the diaphragm during quiet breathing and during full inspiration and expiration; in health the diaphragm is less sharply defined in the latter than in the former.

The lungs usually appear brighter during deep inspiration; in young persons brighter than in older persons, as the tissues of the former are more easily penetrated by the rays. In the thin, the lungs appear lighter than in the heavy, because the outlines are dulled, as it were, by a thicker layer of tissues which contain much water. It has seemed to me that the right apex is normally darker than the left apex. The normal brightness of the lungs and the normal outlines of the clavicles and ribs should be observed, for, as we note different degrees of pallor by reference to our standard of color in health, in the same way is it necessary to know the normal

PLATE II.



The lungs of a patient who died of pneumonia. The lightest portion is healthy. The darker lung has been more affected by the pneumonic process than the lighter.

PLATE III

Tuberculous lung—calcareous pleura, two pieces of which have been separated from the lung and are seen in the upper part of the plate. The calcareous portions of the pleura are dark.

amount of light which should penetrate any given part in order to recognize variations from the normal. The eye must be trained in the use of the X-rays as is the ear for auscultation and percussion, and the fluorescope, like the ophthalmoscope, should be in constant use in order that the practitioner may not lose any of the skill acquired in interpreting the conditions present.

To test the possibilities of an examination with the fluorescope in certain conditions of the lungs, as when congestion or more or less œdema or pleurisy was present, I made one or two simple experiments. On full inspiration in healthy patients I found the pulmonary area lighter than in other stages of respiration, and the ribs stood out in greater contrast, thus showing that there must be less blood in the lung during the former period, and that if any part of the lung is much congested, or if œdema is present, it would naturally appear darker than the normal lung; also when I held a small pasteboard box, about one-half inch deep and full of water, over one side of the thorax of a well-developed and muscular man with a large chest, I could see its shadow in the fluorescope during about full inspiration, but not at other times.

In order to get further suggestions in regard to the possibilities of the X-ray examinations in diseases of the lungs, I took a number of radiographs of healthy and diseased lungs just after death, which were removed from the body and put over a photographic plate. As a specimen of the latter, see Plate II., which shows the lungs of a patient who died of pneumonia. The darker was more affected by the process than the lighter; the lightest portion is healthy. Plate III. shows a tuberculous lung and calcareous pleura. These lungs were kindly sent to me for a few moments by Prof. W. T. Councilman.

Again I examined with the fluorescope, two days before his death, the chest of A. B., one of my patients who died of syphilis, and found his lungs perfectly clear and the outlines well defined. The outlines, also, of the front and back portion of the ribs forming a lattice-work, as shown in the fluorescope, were well seen. The autopsy confirmed the examination made by the fluorescope, and showed that he had perfectly healthy lungs.

We shall see presently that in certain diseases, parts or the whole of one or both lungs appear darker or lighter than in health, and

that their volume may be greater or less than in health. The respiratory excursion of the diaphragm may vary from the normal on either or both sides of the chest, in position—that is, it may be higher or lower in the body, and in amplitude, or it may vary in the curve, or its lines may be wholly or partially obliterated.

In making examinations of the lungs changes in the amount of light seen in the fluorescope should be carefully observed; for example, whether or not one lung is darker than the other. In pathological conditions the indications of change in density, shown usually by diminished brightness, may be estimated by comparing the two sides and observing whether the outlines of the organs and whether the ribs and clavicles are more clearly seen on one side than the other. When both sides are diseased the opportunity for direct comparison with the normal is lost, and one is obliged to

FIG 1.

Chest of normal man twenty-one years old. Examination with fluorescope: the dotted lines on each side of the chest indicate the outlines of the fourth rib; the full lines on either side of the chest about over the fourth rib, the position of part of the diaphragm in expiration; the broken lines just below these, the height of the diaphragm at inspiration during quiet breathing; the full lines below and parallel to these, the outline of the diaphragm during deep inspiration. The full curved line which is near the left nipple indicates the left border of the ventricle during quiet breathing; the full curved line nearly parallel to that, the left border and apex during deep inspiration.

depend upon the recollection of the normal in an individual of the same build. The position, excursion, and curve of the diaphragm should also be carefully noted, as compared with the normal.

In six men with healthy lungs the diaphragm moved over an average range of two and three-fourths inches on the right side and

two and one-half inches on the left side. The maximum excursion in any healthy person I have examined was four inches. In eighteen patients with tuberculous lungs the average excursion of the diaphragm was one and one-fourth inches; in some cases less than half an inch. (Fig. 1.)

Patients may be examined standing, sitting, or lying down, with the rays passing through the body antero-posteriorly or from side to side. Most of my examinations have been made with the

FIG. 2.

patients lying on a stretcher (see Fig. 2), and the Crookes tube on an adjustable holder under the patient. For careful examination of the thorax, for example, the Crookes tube should be about two feet away from the fluorescope, and its position should be determined by plumb-lines, so as to bring it immediately under the

middle of the sternum, on a level with the fourth rib. The fluoroscope is peculiarly applicable to moving organs, such as the heart and lungs, and is useful in examining children.

Let us now take up individually some of the thoracic diseases, and we will first consider pulmonary tuberculosis.

Pulmonary Tuberculosis.

In this the fluorescope may suggest disease in the following ways: First, a diminution in the volume of the diseased lung is shown by the position and movement of the diaphragm; this movement may be less than normal on one or both sides, and will be restricted on the lower side. Second, an increase in density by diminution in the normal brightness, the degree and extent varying in accordance with the increase in, and extent of, the density. The lung may become so dense that no more rays pass through it than through the liver. The brightness or light in the lungs indicates the amount of air in the body.

I have examined more than seventy-five cases of tuberculosis with the fluorescope, and found a correspondence between the physical signs and the X-ray examination in a considerable number of them; in certain cases this instrument showed that the disease was more extensive than the physical examination indicated; in others the fluorescope showed increase in density in the lungs earlier than was detected by the physical examination, and while in some of these no signs in the lungs were detected prior to those found by the fluorescope, in others, although one lung was ascertained by the physical examination to be seriously involved, its companion was not suspected until the X-ray examination revealed its increased density. In most cases of pulmonary tuberculosis the fluorescope enables us to estimate the amount of lung involved better than any other method of examination. Most of the tuberculous patients that I examined at the Boston City Hospital presented well-marked signs of the disease when they entered, but in private practice the proportion of patients who are seen in the early stages, when there is greater opportunity for successful treatment, is larger; and therefore the fluorescope might be of special value in these cases on account of the earlier diagnosis it assists us to make.

The following case shows that the fluorescope detected increase in density in the right lung when it was not found by auscultation and percussion. It likewise indicates the significance of the diaphragm lines in tuberculosis:

H. A., aged twenty years. Tuberculosis(?). Duration, four weeks; family history not tubercular. Medium dry râles at left apex, with slight dulness; right apex normal.

Examination with fluorescope: Left lung exending to level of the fourth rib very dark; there is also some involvement of right apex. The maximum respiratory movement of the diaphragm on the left side is only three-quarters of an inch; on the right side one inch only. This is less than half the normal.

[Later tubercle bacilli were found.]

Let me also give the following case in which increase in density was detected earlier by the X-ray examination than by the other method. I examined this patient because he had a pericardial effusion, but the increase in density at the apex of the right lung was so marked in the fluorescope that it attracted my attention. The usual physical examination was then made, but I could find no evidence of phthisis. I examined the lungs by the fluorescope from week to week, and saw that the denser, diseased area extended, while the movements of the diaphragm became less and less on that side. After about six weeks the fluorescope showed that the left lung had become denser at the apex, and the excursion of the diaphragm on this side was also lessened. No signs were found by auscultation and percussion on this side at this time. There has been no cough, the patient is about as usual in weight, and has no night-sweats, no bacilli have been found; but about two months after his entrance to the hospital he reacted very strongly to tuberculin, and the diagnosis of tuberculosis was established. This reaction is of much service in the diagnosis of tuberculosis in men as well as in cattle. Three months after entrance: still no bacilli have been found, although many examinations for them have been made.

There are some cases where the bacilli are found before marked signs in the lung can be detected by the fluorescope; it may be that in these cases the disease begins in the larynx.

Again, a woman twenty years old, unusually well developed and nourished, entered the hospital with phlebitis of the leg. Two of her sisters had died of tuberculosis. By auscultation and percussion

the heart's area, action, and sounds were normal; resonance and respiration good over the whole of both lungs. After she had been in the hospital two weeks an X-ray examination was made, chiefly because I had established the routine of so examining many of my patients. This examination showed that the maximum movement of the diaphragm on the right side was one and seven-eighths inches, and on the left side two inches. The apices of the lungs were darker than normal on both sides, more so at the right apex than at the left. The outline of the heart showed that that organ was smaller than normal. Tuberculin was given, and was followed by a typical and well-marked reaction. The tubercular family history, diminished movement of the diaphragm, increased density at the apices of the lungs, and the small heart all pointed to the diagnosis of tuberculosis, and this was confirmed by the tuberculin test. As yet there have been none of the ordinary symptoms or signs of disease of the lungs, except those seen in the fluorescope.

We can detect an abnormal condition of the lung in some cases of tuberculosis earlier by means of the fluorescope than by auscultation and percussion. How much earlier these signs can be anticipated depends upon the rapidity of the progress of the disease, and this varies in different persons and conditions. Of course, a diagnosis of tuberculosis is not made by the appearances in the fluorescope alone; they simply indicate an abnormal condition of the lungs. I shall consider more fully the use of the fluorescope in pulmonary tuberculosis in another article.

Pneumonia.

I have examined more than fifty cases of pneumonia with the fluorescope, and some of these, as already stated, a number of times, while watching the progress of the disease, and found in a few cases that the lung had not become normal after months. In patients ill with pneumonia the increase in density in the lungs is very marked in the fluorescope during the active stage of the disease, and by its means we may estimate how large an area of the lungs is involved, and by observing the patients at intervals of two or three or more days, as they improve, we may see the dark areas become lighter and lighter, and finally disappear; and we may see

the excursion of the diaphragm, which has been restricted and restricted on the lower side, become gradually longer as the lungs clear up. I have examined patients while they were convalescing from pneumonia, both by auscultation and percussion and by the fluorescope, on the same day, and while by the former I could not detect that the lungs were denser than normal, I was able to recognize the continued presence of abnormal density by means of the fluorescope, and even when this was no longer possible I could still easily see by means of this instrument that the diaphragm did not descend to its normal limit, thus showing that the lung was still in an abnormal state. Later the normal limit was reached. This method of examination enables us to judge better than any other when the lungs have cleared up after an attack of pneumonia, and if we can obtain, by means of the fluorescope, later evidence of the presence of a pathological process during its subsidence than by auscultation and percussion, we may also reasonably expect to recognize its onset sooner, and I am satisfied that we can.

I think that a slight central pneumonia is at times overlooked when its early detection by the fluorescope would sometimes at least prevent its progress to a more severe attack.

During the past winter I have seen three patients where the diagnosis would have been difficult had not the fluorescope led to that of central pneumonia; one of these cases was seen by three physicians, and we all failed to make the diagnosis. The examination with the fluorescope caused me to make a diagnosis of central pneumonia, and the further progress of the case confirmed it.

The following case shows the significance of the diaphragm lines in pneumonia:

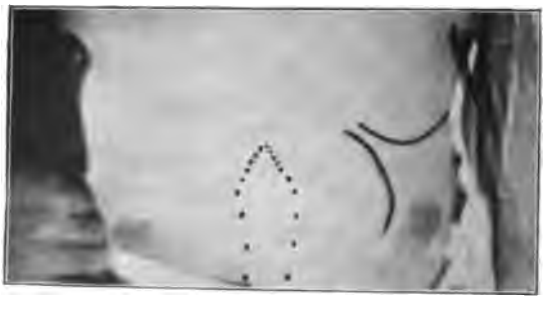
L. B., aged nineteen years. Pneumonia. Examination with fluorescope: on seventh day of disease, right lung dark from middle of first intercostal space to fourth rib; the upper and lower border of this dark area were marked; outlines in chest rather less clear than normal on both sides. Diaphragm moved one-quarter inch on right side, and one and five-eighths inches on left side. Fifteenth day of disease, diaphragm moved one inch on the right side; two and one-half inches on left side. Nineteenth day of disease, diaphragm moved two inches on right side; two and three-quarters inches on left side; original dark area on right side not so bright as other portions of the lung. On the twenty-second day of the disease, diaphragm moved two and one-half inches on right side and three inches on left side.

The abnormal condition of the lungs in tuberculosis and pneumonia may be shown not only by the obstruction which the affected parts offer to the passage of the rays, but also by the restriction of the excursion of the diaphragm. In some cases the latter is a more delicate test.

Pleurisy.

In pleurisy with effusion we can estimate the amount of fluid in a general way by the amount of light which passes through the thorax, and can follow the subsidence of the fluid. When the effusion is large no more rays pass through it than through the liver, and the outlines of the diaphragm, ribs, and heart are obliterated on the side of the effusion. If there is a smaller amount of fluid, the outlines of some of the upper ribs are seen, and with a small effusion the outlines low down in the thorax only are ill-

Fig. 8.



Pleurisy, with effusion on the left side; heart displaced to right. Curved lines indicate the right border of the heart and the upper border of the diaphragm.

defined. The fluorescope assists us to distinguish between an effusion and a thickened pleura. In some cases of effusion the fluorescope shows us displacement of the heart, to the left when there is a large effusion on the right side and a much greater displacement to the right, and this displacement is of more frequent occurrence when the effusion is on the left side. This displacement of the heart to the right may not be recognized by percussion even when it has been pushed much beyond its normal place. In one patient the heart was seen to be displaced more than two inches to the right, but no

displacement was detected by percussion. While examining some cases of pleurisy with effusion by the fluorescope I have found indications of tuberculosis in the lung where it was not previously suspected.

Emphysema.

In emphysema we see in the fluorescope that the lungs are unnaturally clear and their volume is increased. The heart is seen in the fluorescope more clearly than normal, although by percussion the true outline cannot be determined. The diaphgram is seen to be lower than normal, and the excursion which it performs between deep inspiration and expiration to be less than normal. The heart

Fig. 4.

Emphysema. Dotted line marks cardiac area by percussion; full line by fluorescope. Diaphragm lines, in expiration and inspiration, are shown on each side of chest below the nipple; they are lower and nearer together than normal. The broken line below inner end of left clavicle shows arch of aorta.

also may lie lower than in health, and in the later stages in a more vertical direction. In some cases the emphysematous condition may be greater on one side than the other. The lower position and the more limited excursion of the diaphragm give a means of making a diagnosis of this condition probably earlier than has hitherto been possible, or in some cases the lack of these signs assures us that no serious amount of emphysema is present.

The following case was sent me with a diagnosis of emphysema with asthma:

B. F. Examination with fluorescope: diaphragm moved on the right side two and one-half inches and on the left side three inches. The excursion of the diaphragm being normal, indicates that there can be but slight emphysema present.

I have seen patients, both young and old, who complained of getting out of breath on exertion, and the cause in some cases would have been obscure but for the fluorescope, which showed that the dyspnœa in both young and old was due in some instances to emphysema, and in others to œdema of the lungs.

If some other disease is associated with emphysema, as, for instance, some form of bronchitis, the excursion of the diaphragm is characteristic, but the abnormal clearness of the lungs may be wanting.

Bronchitis.

The appearances of bronchitis in the fluorescope vary; they may differ very little from those in health, or both sides of the thorax may be less bright than normal. The respiratory movement of the diaphragm was not especially impaired in the cases I have seen.

Pneumothorax—Hydrothorax—Pneumo-hydrothorax—Œdema of the Lungs.

In pneumothorax the fluorescope shows that the affected side of the chest is lighter than normal, that the heart and vessels may be much displaced, and the diaphgram much lower than normal on that side, and that it has a characteristic curve. In pneumo-hydrothorax or pneumo-pyothorax, when the patient is examined lying down, the whole of the affected side of the chest is seen to be dark; if examined in a sitting position, the upper portion of the chest is clear and the lower dark. The appearances remind one of a tumbler half full of ink; when the patient bends forward or backward the height of the fluid on the chest-wall changes; if the patient is shaken gently, the surface of the dark fluid is seen to be agitated. In pneumo-hydrothorax or pneumo-pyothorax on the left side the surface of the fluid is seen to be disturbed by the pulsations of the heart.

In hydrothorax and œdema of the lungs the fluorescope is also of service. In these conditions, as well as in empyema, the outlines of the diaphragm are wholly or partially obliterated. Some partial œdema of the lungs is, I am inclined to believe, a more frequent condition than has been supposed. On first examining a patient of this class, his condition being unknown, I was surprised to find how difficult was the passage of the rays, and when I saw that the picture of the patient's thorax in the fluorescope was unusually dark, supposed something was wrong with my Crookes tube; but after trying another I realized that the patient's chest was denser than normal; the tube was not in fault. I have examined a number of cases which illustrate the aid the fluorescope renders in congestion or œdema of the lungs; this instrument showed that one of these conditions was present when it was not made out by physical signs; and thus assisted in estimating how much the pulmonary circulation was interfered with in cardiac or renal disease.

I have found it instructive to study, by means of the fluorescope, cases of dyspnœa on exertion and note the amount of congestion or œdema of the lungs present in them. Cases of this kind have already been referred to under emphysema.

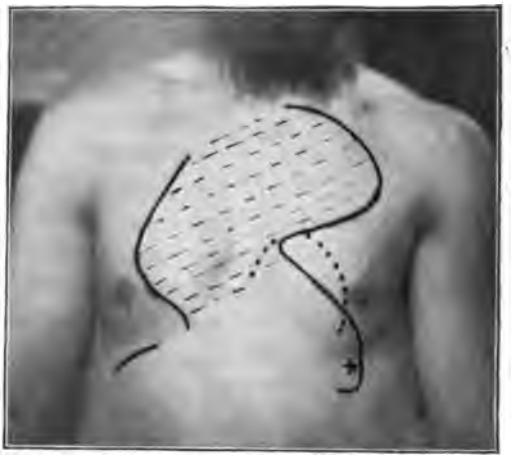
H. E., aged twelve years. Entered the hospital with an old endocarditis following rheumatism. There was a systolic souffle at the apex of the heart transmitted to the axilla; enlarged heart; orthopnœa, œdema of the lungs, and intense dyspnœa. Digitalis given. Three days after entrance examination with the fluorescope showed that the lungs were denser than normal below the second rib on the right side and the third rib on the left side. Four weeks later second examination with fluorescope: Lungs perfectly clear, heart smaller. The patient had been up and about for some time.

Aneurisms.

I have examined with the fluorescope and taken radiographs of one subclavian and several thoracic aneurisms. The heart in some of these cases was much displaced. Aneurisms of the arch of the aorta are most clearly outlined when their borders are nearest the fluorescope; those on the left when examined from the back, those on the right when examined from the front. It is obvious that aneurisms of the thoracic aorta can sometimes be detected earlier by X-ray examination than in any other way. In obscure thoracic

cases, where an aneurism of certain portions of the aorta is suspected but does not exist, it may probably be excluded by an X-ray examination.

FIG. 5.



Examination with fluorescope: the curved line in the upper part of patient's left chest and the curved line on his right chest indicate the outline of the aneurism as seen in the fluorescope. The lower curved line on the left chest marks the outline of the heart; the lowest curve on the right front, part of the outline of the diaphragm. The dotted line, the cardiac area as determined by percussion. This case shows how a large aneurism may exist in the chest without giving rise to marked physical signs.

I have recently seen in consultation a patient who had had excellent advice in Boston and New York, as well as elsewhere, and the diagnosis was obscure until my X-ray examination showed an aneurism of the aorta; in another case my X-ray examination showed that there was no aneurism where it was thought to exist.

THE HEART.

Let us now consider the size, position, and movement of the heart in health as shown by the fluorescope, before taking up some of the applications of the X-ray examinations in cardiac diseases. The best view of the heart is obtained during full inspiration, as then the diaphragm is so depressed as to expose a much greater part than during quiet breathing, and with more air in the lungs the outlines of the heart stand out better on account of the greater contrast thus produced; on the left side of the sternum the objects seen most

FIG. 6.

FIG. 7.

Figs. 6 and 7 show a smaller aneurism of the aorta. The arrow in Fig. 7 points to where the pulsation was best seen.

clearly are a considerable part of the ventricle, including the apex and the pulmonary artery; on the right of the sternum the right border of the venæ cavæ and a large part of the right auricle.

When the space occupied by the lungs is in a normal condition the outline of the portion of the heart on the left of the sternum can

be followed by means of the fluorescope with more certainty, accuracy, and more fully than by percussion. The lower border of the heart near the apex is not obtained by percussion, but part of it is seen in the fluorescope during deep inspiration. Also, on the right of the sternum the position and size of the right auricle, although it is not distinctly outlined, can be better ascertained by the fluorescope than by other means; likewise the right border of the venæ cavæ, which is much more marked in the fluorescope than the right auricle; but the right border of the ventricle, being behind the sternum in health, is then better determined by percussion than by the fluorescope.

The position of the heart varies in health in different persons. With deep inspiration it may move downward and toward the median line nearly an inch. While watching the pulsations of the heart in the fluorescope I observed that the most marked changes in the outlines were not at the apex, but in those on the left side at the point corresponding to the cavity of the ventricle, the maximum pulsation being about where the outline of the ventricle crosses the fourth rib. I could see the ventricle contract and expand as it emptied and filled.

The change in the position of the heart, due to conditions outside of itself, such as pleurisy with effusion, pneumothorax, emphysema, etc., may be seen in the fluorescope, as already stated, or the change in position due to its own enlargement. We may also recognize, for example, enlargement of the ventricles and see a dilated right auricle and pulsations and enlargement in the venæ cavæ. Differences in size may likewise be observed; for instance, the diminution which is found in anæmic patients with tuberculosis, or increase in size which takes place in hypertrophy or dilatation.

The ability to observe such changes as the above enables us to obtain a more accurate knowledge of the condition of the heart in disease than has hitherto been possible.

The so-called apex-beat, which physicians use so much as a point of reference in examining the heart, is not the apex-beat in all cases, but sometimes an impulse given by the side of the ventricle; the apex of the heart is then seen in the fluorescope to be lower down, usually much below the point where the impulse is felt on the wall.

Calcareous deposits may be seen in some cases, but at present only

when the disease is unusually well marked. In one of my patients I saw a dark area in the aorta and in portions of the heart contiguous to it which were pushed over to the right of the sternum. The autopsy showed that this dark area seen in the fluorescope was a calcareous deposit.

The fluorescope assists us to make a differential diagnosis between a pericardial effusion and an enlarged heart. Not only are the outlines seen to be different in the two cases, but in pericarditis with much effusion the characteristic pulsations of the heart are not seen.

In some diseases the outlines of the heart to the left of the sternum, as found by percussion, are not correct. In order to compare the size and position of the heart, as obtained by this method and as seen in the fluorescope, I drew on the skin the cardiac outlines found by percussion, and directly afterward these outlines as seen in the fluorescope. I have done this in about thirty cases. Both sets of outlines were then traced on tracing-cloth, held carefully over the skin, the one in red and the other in blue lines. (In other patients I photographed the two sets of lines.) Comparison between these lines showed that in some cases the outlines obtained by the two methods, namely, by percussion and by the fluorescope, agreed very well; in others the difference was marked. It should be stated, however, that although percussion does not indicate in some cases the true size and position of the heart, a proper examination of this organ with the fluorescope is difficult to make, needing careful adjustment of the X-ray apparatus and experience with a considerable number of cases.

I have used several methods for recording the outlines of the heart seen in the fluorescope; one record is made by means of a flexible fluorescent screen which has a smooth surface like a porcelain slate. The screen is placed on the chest of the patient, the room is darkened, and the outline traced with an ordinary lead-pencil. These lines may be afterward rubbed out with a moist sponge, and the screen used again. Another method, alluded to above, and one which allows of a ready comparison of results, is to draw the outlines of the organs on the skin by means of a special pencil, while looking through the fluorescope, and then to place a piece of tracing-cloth, about a foot square, on the chest, and trace upon it the outlines that have been drawn on the skin. It is well in these tracings to include the sternal

notch, the nipples, the fourth rib, the ensiform cartilage, and the border of the ribs on either side and below the latter, as these serve as points of reference and comparison. Care must be taken that the tracing-cloth be held smooth and that the skin be not moved or stretched. These cloth tracings may be placed one over another and readily compared, as, for instance, the abnormal with the normal, or the size and shape of the heart in different diseases or at various times in the same disease.

In the mediastinum new-growths or abscesses may be expected to give evidence in the fluorescope of their presence by displacing the vessels and changing the normal outlines of the latter before they are large enough to be themselves seen by means of this instrument.

I wish to point out the advantages that will follow a study of carefully made radiographs. I have taken radiographs that indicate, for example, adipose tissue, the outlines of muscles, tendons, and arteries in healthy persons, both children and adults.

Summary.

No harmful effects have been received by the patients—more than five hundred in number—that I have examined with the X-rays.

The varying resistance which the different tissues of the body offer to the passage of the Roentgen rays depends upon difference in bulk and in chemical composition.

The difference in permeability of air and water by the X-rays is of great importance in thoracic diseases.

The normal brightness of the chest having been observed in the fluorescope, the departure from the normal in two directions may be noted by comparison. First, a given part of the chest may be darker than normal on account of the obstruction offered to the passage of the rays, which is due to the increase of density that occurs in tuberculosis, pneumonia, infarction, œdema, congestion of the lungs, aneurisms, new growths, or to fluid in the pleural and pericardial sacs, that occurs in pleurisy with effusion and pericarditis with effusion; the distribution, location, and amount of this increase in density, which the fluorescope shows, assist us in some

cases to distinguish between these diseases or conditions. Second, a given part of the chest may be brighter than normal, because it is more permeable than in health by the rays, on account of the diminution in density, due in the case of emphysema to increase in the amount of air in the lungs, or, in the case of pneumothorax, to increase in the amount of air entering the pleural sac and displacing the lung.

Importance of the diaphragm lines: the normal diaphragm lines on both sides of the chest (these include position, excursion, and curve of the diaphragm and the clearness with which they are seen), having been observed in the fluorescope, departure from the normal may be noted by comparison. In tuberculosis and pneumonia the excursion of the diaphragm is restricted, and restricted on the lower side; in emphysema, on the contrary, although the excursion of the diaphragm is restricted, it is restricted on the upper side—the diaphragm goes lower down toward the abdomen—and in pneumothorax, on the affected side, it has a characteristic curve and moves only on its median end. In tuberculosis, pneumonia, pleurisy, hydrothorax, empyema, and œdema of the lungs, the diaphragm lines, as well as those of the heart, may be wholly or partially obliterated. In some cases of tuberculosis and pneumonia the lessened range of movement of the diaphragm is a more delicate test than the diminished brightness of the lungs. The normal outlines of the diaphragm may also be changed by an abscess or a new growth contiguous to it.

The fluorescope gives us better assurance that the lungs are in a healthy condition than other methods of physical examination.

The fluorescope, in connection with auscultation and percussion, teaches us to interpret better the signs found by the older method.

The fluorescope gives us earlier evidence of disease in some cases of tuberculosis and more accurate information of its extent (this affects the prognosis) than can be obtained by the usual physical examination.

The fluorescope gives us more accurate information of the extent of the disease (this affects the prognosis) in pneumonia and of the duration of an abnormal condition of the lungs.

The fluorescope shows a displacement of the heart in pleurisy

which is sometimes not recognized by other means, and assists us to recognize and estimate the amount of fluid in the pleural and pericardial sacs.

The fluorescope enables us to recognize or exclude emphysema.

The fluorescope enables us to make a diagnosis in some cases of dyspnœa that would otherwise be obscure.

The fluorescope assists us to recognize œdema of the lungs, pneumothorax, hydrothorax, and pneumo-hydrothorax.

The fluorescope gives us the means of making an earlier and more certain diagnosis of some cases of thoracic aneurism than any other method.

The fluorescope enables us to outline the heart more accurately and completely than has hitherto been possible and to observe certain changes in it; and it especially assists us to a more accurate determination of the size, movement, and position in disease, and in some cases to observe not only the heart as a whole, but the auricle and ventricle separately. Further, it enables us to recognize earlier associated conditions, such as œdema of the lungs, and assists us to recognize pericardial effusion.

We may sometimes make a diagnosis by an X-ray examination alone, in certain cases of aneurism and emphysema, for example, but it is, as a rule, only one method of examination and its value in assisting us to establish a diagnosis varies, of course, in different diseases. The X-ray examination should be used in connection with other methods; the information derived from it in suitable cases is more definite and accurate than that obtained from auscultation and percussion. I now use the fluorescope in my office as I do the stethoscope; both are valuable instruments and aid each other.

As is the case with all other observations on which a diagnosis is founded, the conditions which are revealed by the fluorescope are only to be rightly interpreted after experience in making X-ray examinations has enabled the physician to gives these observations their proper weight.

I have had the privilege of studying the physics of the X-rays in the Rogers Laboratory of the Massachusetts Institute of Technology, and I am under obligation to Professor Charles R. Cross and two

of his assistants, Mr. C. L. Norton and Mr. R. R. Lawrence, for their co-operation in my study. I also desire to express my appreciation of the active interest taken by the trustees of the Boston City Hospital in my work, and the kindness of my colleagues on the staff for affording me an opportunity of examining many of their patients.

SOME OF THE UNTOWARD EFFECTS PRODUCED BY THE ADMINISTRATION OF THE BROMINE COMPOUNDS.

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It is not my intention to discuss in this paper the well-known untoward effects of the bromides as they are manifested by eruptions on the skin, mental torpor, and the final development of a cachexia and general as well as nervous feebleness. The conditions on which I desire to dwell are more unusual and not so well known to the profession, although they are more common than would be supposed.

In the study of remedies, both old and new, the tendency of the physician is rather to record his successes than his failures, and to report the instances in which the drug has done good rather than those in which it has failed or done harm. It is only after many years of experience roll by that the profession gains a complete view of the reverse of the therapeutic shield. The untoward or unexpected effects of drugs are, however, never to be forgotten, and the possibility of a remedy causing an unusual symptom is to be ever borne in mind.

At a meeting of the Association of American Physicians held in Washington in May, 1896, Weir Mitchell read a paper detailing a number of instances in which the use of the bromides had speedily produced a number of untoward effects over and above the skin eruption, disordered digestion, and mental slowness usually met with after full doses of this drug are used. Thus the symptoms manifested consisted in great irritability of temper, moroseness, and homicidal or suicidal tendencies. In one case, that of Jacksonian epilepsy in a child, imbecility developed from the use of bromides, another child became a sufferer from amnesic aphasia, and in an adult female

suicidal tendencies and melancholia appeared when the drug was used and disappeared when it was stopped. Voisin and Stark reported cases many years ago, and Harriet Alexander as recently as July, 1896, has contributed a valuable paper on this topic, in which she reviews the literature on this subject in this country quite thoroughly. Seguin reported the case of a twelve-year-old boy who had *petit mal* in the form of chills, and when these were stopped by the bromides he became unmanageable and boisterous. Hughes, of St. Louis, has reported another case of *petit mal* which developed kleptomania when the bromides were given, and Rockwell has recorded an instance in which an epileptic female on taking the bromides became irritable and suspicious.

Dr. Alexander, in the paper quoted, cites several instances from an earlier contribution of hers on this subject. An epileptic nymphomaniac always became irritable and suspicious on the use of the bromides. In another woman, with a family history of epilepsy and imperative homicidal conceptions of long-continued form, erotico-religious, auditory and visual hallucinations followed the use of the bromides. In another female troubled by coprolalia the bromides caused sullenness and unrestrained coprolalia. In still another case the bromides caused an irritable, suspicious state in which the patient became treacherous. A ten-year-old girl with progressive epilepsy, had three attacks replaced by irregular kleptomania attacks, and she became suspicious and irritable. The last three cases reported by Alexander are particularly interesting. They are as follows:

A female; has *petit mal.* She denies all epilepsy. Long after her marriage, epilepsy, although it clearly existed, was never suspected until she awoke her husband one night by beating his face with a slipper while unconscious. In the inter-epileptic period she is mild-tempered, good-humored, and suave. Under the bromides she becomes first irritable, and querulous during the inter-epileptic period, then paroxysmally furiously excited, and has vivid auditory and visual erotico-religious hallucinations, and is coprolaliac. Mixed treatment has no such effects.

Since then Alexander has observed the following cases:

A thirty-four-year-old woman had *grand mal*, followed by a dazed condition. Under the bromides these attacks were replaced by

nymphomania with decided erotic manifestations, attended by religious hallucinations and furious masturbation. The use of ergot removed these manifestations, and the alternation of ergot with the bromides prevented them.

A forty-two-year-old woman had attacks of *grand mal* at the menstrual period and *petit mal* in the interregnum. These were both replaced by furor under the bromides.

Similar instances have been reported by Janeway, Dana, and Draper, and the older literature of medicine shows that these unusual effects were not unknown and are not now met with for the first time. Many years ago Hammond recorded the case of a gentleman to whom he gave at first fifteen grains of potassium bromide three times a day. These doses, which were slightly increased, soon produced symptoms of mental aberration, which disappeared when the medicine was stopped. Later the patient of his own free will insisted upon taking as much as one ounce of the drug a day. He developed marked insanity, delusions of persecution, and the delirium of grandeur. He became timid and cowardly, and finally so insane as to necessitate his removal to an asylum, in which recovery took place. In other cases hallucinations as to sight or sound have come on without there being any alcoholic history to complicate the case.

Bannister has also reported a condition of pleasurable intoxication with exaltation of mind after doses of bromide. Thus he reports the case of a man of thirty-six years of age who was a sufferer from frequent epileptic attacks and had slight mental impairment, but no true psychic disorder and no delusions. He was regarded as a quiet, well-behaved patient, except when the bromides were given him, when he became furiously excited and unsafe. Thus before commitment to an asylum he had been convicted of homicidal tendencies. Small doses of the bromide rarely brought on the attacks except after several days, but as much as one and a half drachms daily made him unmanageable in three or four days. Stopping the bromide stopped the mania but allowed the return of the attacks. Bannister reports other cases, three in all out of twenty-one epileptics under his care.

This and the following report of cases illustrate the clinical fact that the arrest of epileptic attacks by full doses of the bromides produces on rare occasions evidences of nervous excitation in other

forms. Thus Baker in the *Medical Register* of December 8, 1888, reports the case of a man of eighteen years suffering from many convulsions each day who was said to be unable to take the bromides. Nevertheless, he was put on fifty grains a day. This resulted in an arrest of the attacks, but they were supplanted by noisy outbreaks of ungovernable rage, but no delusions. Another case of a young man was met with who had maniacal delusions which always disappeared if the bromides were stopped and the attacks allowed to return. A third case experienced mental confusion when the bromides stopped the attacks. Lepine also reports a case (*La Semaine Médicale*, December 23, 1891) of a tabetic young woman who received sixty grains of bromide a day for convulsive attacks. In the course of a few weeks she became progressively weaker and delirious, and Lepine believes that difficult speech, delirium, and mental weakness often follow the use of bromides.

Holmden, in *The Lancet* of October 18, 1886, also reports the case of a sailor, aged thirty-three years, who was in the habit of taking three drachms of bromide of potassium a day for the purpose of relieving insomnia, and who began to develop delusions and to be unable to collect his thoughts. Notwithstanding advice to the contrary, he persisted in the use of the drug and developed delusions of persecution, maniacal symptoms, and suicidal tendencies, followed by great prostration. Recovery ultimately occurred.

Hameau (*Journal de Médecine de Bordeaux*, March, 1868) has reported the case of a young woman of twenty-two years who, after taking no less than four and a half pounds of bromide of potassium in ten months, developed cachexia, delirium, and after great prostration she died.

We have also the report of Eigner in the *Wiener medicinische Presse*, Nos. 25-34, 1886, who records the case of a woman who took five pounds in a year, and after developing the ordinary symptoms of bromism developed tremor, a staggering gait, followed in a few hours by excitement passing into delirium with delusions of poisoning.

Thompson, in *The Lancet* of May 11, 1889, asserts that he has frequently seen cases of maniacal insanity produced in feeble-minded persons and in the insane by drenching them with bromides. He does not, however, report any definite cases.

Gaston Lyon, in his *Traité Eléméntaire de Clinique Thérapeutique*, 1895, says in some cases the bromides have to be stopped when given to epileptics, as they either increase the number of the attacks or, if they stop them, bring on cerebral disturbances.

Marked untoward effects of the bromides are recorded by Souillier (*Traité de Thérapeutique et de Pharmacologie*, Paris, 1895), who states that in those instances in which a bromide cachexia develops there are, in addition to feebleness, commencing paralysis of the lower extremities, tremors, coldness, anorexia and diarrhœa, loss of intelligence, memory, and sometimes delusions, hallucinations, headache of an intense kind, and dilatation of the pupils. He quotes Le Gender as having seen instances in which the bromides in overdose caused in epileptics symptoms simulating typhoid fever.

Laborde (*Gazette Médicale de Paris*, 1886) has seen sexual excitement follow the bromides, and Winters has reported visual hallucinations (*New York Medical Journal*, 1883). Alexander also quotes Kiernan and Monroe (*Medical Standard*, 1887 and 1891) as having met with cases of aphrodisia from this drug.

One conclusion seems certain beyond doubt, that in many cases of epilepsy the bromides are very capable of causing grave injury aside from the general depressing influence which they excite in all persons if given in full doses for any length of time.

In other instances in non-epileptic patients the use of the bromides has produced aphasia and apyrexia. Thus Lockhart Clarke has recorded an instance of a patient who said "contraction" for "subscription," and E. H. Clarke one who called a buckwheat-cake a comb, and a comb a buckwheat-cake.

With the idea of gaining additional information about such important variations from the uusal manifestations of the action of the bromides the writer addressed the following letter to a number of well-known neurologists and to physicians in charge of insane asylums:

DEAR DOCTOR: Within the last few months my attention has been called to the fact that the administration of bromide of potassium to certain persons, either sane or insane, produces a mental alienation or influences unfavorably the manifestations of insanity already present. I am trying to find out whether the experience of one or two gentlemen has been duplicated by others having such a wide experience as you must have had. I enclose a set of questions designed to elucidate this point, and shall feel personally

obliged to you if you will be good enough to answer as fully as you feel inclined the questions that I enclose.

The questions were as follows:

1. Have you noticed in your practice that the administration of the bromides in full doses ever produces mental alienation or true delusions?

2. If so, have the symptoms of the patients been those of sedation or excitement?

3. Has a single full dose ever produced such symptoms?

4. Do you think that such untoward effects of the bromides are more commonly met with than is generally thought?

The answers I have received are as follows as to Question 1:

Dr. H. M. Bannister, of the Asylum at Kankakee, Illinois: "I have seen epileptics who were rational and quiet made violently maniacal. This was directly induced by the bromides. I have also seen pronounced hebetude and mental depression caused by their use. As regards the production of true delusions by the bromides, I cannot speak definitely any further than to say that I believe the causeless violence and the deep depression are both probably attended with false conceptions."

Dr. John B. Chapin, of the Pennsylvania Hospital for the Insane, Philadelphia, answers Yes; that he has seen mental alienation and true delusions follow the use of the bromides, and in an article by this author read before the Association of Medical Superintendents of American Institutions for the Insane in 1891, he records a number of cases closely allied to those under discussion, in which the use of the bromides with other drugs, such as chloral and morphine, produced delusions or maniacal excitement. Thus in one case a man was brought to him with "acute maniacal fury," who had received fifteen grains of bromide of potassium every three hours for a time not stated, and chloral twice a day. The symptoms ceased when the drugs were stopped.

Dr. E. N. Brush, of the Sheppard Asylum of Maryland, states that he has seen "in many instances mental confusion ranging from simple hebetude to low, muttering delirium induced in epileptics by the administration of bromides, conditions which have cleared up when the drug was stopped." He also says: "It is very common in institutions to receive cases, clinically very much like what has

been described as confusional insanity, in whom either depression or melancholia predominated, complicated by restlessness and excitement, sometimes conditions simulating delirium tremens, who have rapidly cleared up and made a good recovery when the bromides were discontinued and full diet, attention to disturbed digestive functions, often aggravated by the use of bromides, and ferruginous tonics have been administered. It is very easy to appreciate the reasons for all this. The patient at home has been restless and excited, as the result of mania or of melancholia with apprehension, and sleepless, as is almost always the case in the various forms of alienation in the acute stages. The family physician has naturally endeavored at the same time to quiet the patient and allay the worry and anxiety of the family incident to the patient's restlessness, and has considered the bromides as the best therapeutic means to accomplish these results. Much of this has grown out of the unfortunate teaching of a few years ago, as a result of which very many practitioners have the idea that all forms of insanity depend upon the cerebral hyperæmia, and that bromides in one form or another have the property of controlling this and producing sleep." He cannot recall a single instance in which mental alienation or true delusions followed or were apparently caused by bromides, if the patient was of sound mind before the drugs were given.

Dr. Richardson, of the State Asylum at Columbus, Ohio, in an experience of over twenty-five years and 6000 cases, cannot recall an instance in which the bromide has caused insanity in a previously sane person.

Dr. James G. Kiernan, of Chicago, answers this question in the affirmative, and adds that it should be understood that he refers in his replies to the untoward action of potassium and the alkaline bromides on the sane, exclusive of epileptics.

Dr. W. Brown Ewing, Physician of the State Asylum for the Chronic Insane at Wernersville, Pa., says he has not met with any disagreeable symptoms.

Dr. John W. Ward, Chief Physician to the New Jersey State Hospital for the Insane, replies as follows: "I take it for granted that you mean the bromides of potassium and sodium especially, and in reply, first, I would state that we have never had any symp-

toms of mental alienation following full doses of the bromides. We have used the bromides, and particularly bromide of potassium, in large doses for the last twenty-five years in this institution. We give it nowadays almost always to epileptics—at least, we regard it as the best remedy, either singly or in combination, in the cases of epilepsy that come under our care. The only ill results we have noticed in this hospital is a breaking down of the system as manifested by disordered digestion and pimples on the face where there is long continued use. This we have often obviated by associating the bromide with tonics in its exhibition—not always, but usually so—so much so that in nearly all, or quite all, the cases where now we propose its use for a continued period we associate it with the tonics. Apart from this, however, we have never noticed any injurious effect following its use, even when giving twenty-five and thirty-grain doses three or four times daily for a period of months. I may state, however, that I have seen decided symptoms of dementia, in a few cases, follow the use of chloral hydrate. It occurs to me that this is possibly the case in the instance mentioned by your friends to which you refer. Where mental alienation has followed the use of the bromides, they may have been exhibited in association with chloral, as seems to be the fashion now in some sections. Under no circumstances do we ever administer chloral and bromides of potash or soda together. We have not infrequently had cases brought to us described as having the bromide-habit, but in each and every case I have found that morphia was associated as a quieting agent with the bromide, and in such cases the morphia-habit did exist, but the bromide-habit did not. After exhibiting the bromides for months, we have been able to withdraw it at once without any evidence of any particular habit having been formed for it, or in any craving after the drug. When the bromide of potash was heralded in our magazines as a remedy for the habit of masturbation, I gave it in large doses, with no bad effect following it, except in a few cases where it produced so-called bromide intoxication. This followed the exhibition of the drug in sixty-grain doses four times a day for several days in succession, with no particular benefit so far as the habit was concerned, but with a decided muscular weakness and trembling and inability to walk, and in a few cases inability to co-ordinate the movements, much the same as in progressive loco-

motor ataxia. In each and every case, however, where such a result obtained, the patient soon rallied and regained his usual ability to walk in a few days after the exhibition of the drug was suspended.

Dr. H. A. Hutchinson, Superintendent of Western Pennsylvania Hospital for the Insane, Dixmont, Pa., says: "In answer to your letter I may say that I have never noticed any peculiarity in a patient following the administration of bromide, other than the depression which is seen where it is pushed for a long time. I have never seen any delusions or other symptoms produced. We use but little bromide in this institution, almost none at all, and for years past my experience with this drug has amounted almost to nothing."

Dr. H. E. Allison, Medical Superintendent of the Matteawan State Hospital at Fishkill Landing, New York, says: "We seldom administer bromides in full single doses except in cases of great mental disturbance or in epileptic status. There are some few cases of epilepsy now which are receiving the bromide regularly in doses varying from thirty to sixty grains a day (ten to twenty grains three times daily). In occasional instances we have prescribed the mixed bromides. We have not noticed any mental alienation of true delusions which we could directly ascribe to the influence of this drug used in this manner.[1] It is true that many epileptics possess delusions and that many pass into states of dementia; but these conditions arise irrespective of the use of the bromides, as there are certain patients here who possess delusions and who have not been put upon the bromide treatment. We have had one or two cases of brominism from the prolonged use of the drug, evidenced in the acne and in the dull, lethargic state of the patient."

Dr. Robert H. Chase, of the Friends' Asylum for the Insane, Frankford, Philadelphia, says he has seen the effects asked about in Question 1, and cites the following case: "Several months ago I was asked to see a young man, with view to having him placed in the asylum. He was an epileptic, who had been taking the bromides under the direction of a 'travelling physician,' who lived at a distance. When I saw him he was in an epileptic furor, irritable and excitable, with persecutory delusions. I directed them to dis-

[1] In non-epileptic persons Dr. Allison has, however, seen excitement follow the bromides. See his answer to Question 4.

continue his medicine, and ordered him to Atlantic City, where he rapidly gained lucidity and composure."

Dr. G. Alder Blumer, of Utica, has not met with symptoms of excitement, but he asserts that much harm is done by the indiscriminate use of the bromides.

Dr. L. Pierce Clark, of Craig Epileptic Colony of New York, replies: "I have never found any delusions produced by the administration of full doses of bromide. The character of mental alienation that I have most frequently noticed is that of dementia."

In answer to Question No. 2 Dr. Bannister states that symptoms of sedation and excitement were both present. In epileptic cases the excitement was marked rather than depression.

Dr. Chapin replies: "Sedation, mental hebetude, and subacute delirium." But in the report already quoted he cites cases of excitement.

Dr. Brush evidently thinks the symptoms are those of sedation rather than excitement. Dr. Richardson says that it decreases mental activity.

In answer to this question Dr. Kiernan says the types are, as a rule, those of exhaustion, resembling acute hallucinatory confusional insanity; sometimes they are stuporous; very rarely emotional and exalted.

Dr. H. R. Allison has not met with excitement after the use of the bromides, but has with sedation, for he says: "We have administered the bromides usually in combination with chloral, in large single dose, to cases suffering from a quick succession of epileptic seizures—that is, to patients who were in the *status epilepticus*—and in such cases we believe that we have produced beneficial results by its administration, as the seizures have ceased and the patient passed into a quiet state, emerging therefrom exhausted, but afterward progressing to a state of consciousness and ordinary health."

Dr. Chase replies that the symptoms have sometimes been those of sedation, sometimes of excitement: "All the effects that I have ever noticed from the administration of bromide have been of sedation."

In answer to Question 3, few gentlemen have met with a case in which a single dose of bromide has had the effect of producing mental disorder.

Dr. Kiernan states that he has seen stupor, acute hallucinatory types, and emotional exaltation resembling hypomania.

Dr. John W. Ward says: "I have never seen any ill effects whatever follow the exhibition of single full doses, say sixty grains of the bromides. In most cases it is tranquillizing. Sixty grains, however, we regard as an exceptionally large dose. Our usual standard dose, either as a tranquillizing agent or as exhibited to our epileptics, is from twenty to twenty-five grains, and repeated not oftener than three times per diem."

Dr. H. R. Allison says: "I am not aware that a single full dose of bromide has in our instances occasioned excitement, as it is only when such conditions of excitement prevail that the drug is administered.

Dr. Chase has never seen such effects follow a single dose.

Dr. L. Pierce Clark states: "I have seen a single large dose of bromide produce temporary amnesia, which in a measure simulated the more permanent dementia seen after its prolonged administration."

In answer to Question 4, Dr. Bannister writes: "Yes, decidedly so, when large doses are given; not often with moderate doses carefully used."

Dr. Chapin also makes the same statement in the report already quoted.

Dr. Brush says: "For years I have been decidedly of the opinion that the administration of the bromides is subject to abuse on the part of the profession, and that untoward effects are much more common than are realized. . . . I have made it a point for fifteen years to call attention to the dangers incident to the careless administration of the bromides."

Dr. A. B. Richardson, of Columbus State Hospital of Ohio, believes that the bromides tend to produce an increase in the dementia and hasten the degenerative process in epileptics, and he is much opposed to the use of the bromides in insanity, as he thinks it impairs nutrition and the blood.

Dr. Kiernan thinks these effects are common.

Dr. W. Brown Ewing says: "Have never noticed any bad effects from the bromides. When long continued I always give two or three drops of Fowler's solution, as in epileptics. My experience is that the insane do not show the rash as soon as the sane."

Dr. John W. Ward says: "An opinion based on our experience here would lead me to think, as has already been stated above, that no untoward effects ever follow the use of the bromide, other than breaking down already referred to in answer to Question 1."

Dr. H. R. Allison makes the following interesting reply to Question 4, interesting because it to some extent modifies the view obtained from reading his reply to Question 1: "There is a condition of excitement which I believe is produced by the excessive use of bromides usually combined with chloral in persons who are not epileptics but who are simply suffering from mental disturbance, constipation, and lack of nourishment, which often occur in cases recently admitted. Histories in such cases often indicate that the patient has been systematically drugged with large amounts of both bromide and chloral, and that too little attention has been paid to other features of the disease, apparently relying upon large doses of sedatives to produce calmative results. By reference to our prescription list I find that there are but six patients out of a population of 575 who are at present regularly taking bromides, and the house is almost entirely free from exhibitions of noisy excitement."

Dr. Chase thinks the bromides are abused.

Dr. L. Pierce Clark: "I think that untoward effects of the administration of bromide are much more frequently produced than is thought by the profession at present, although at times it is difficult to say just how much mental alienation is produced by its administration, because the epilepsy itself has a tendency to produce mental symptoms almost the same as those obtained from the administration of the drug."

In the discussion of Dr. Mitchell's paper the author of this article brought up the question as to whether the depressant and other harmful effects of the bromides were in a certain number of cases due to the potassium base, and later discussed it in the editorial columns of the *Therapeutic Gazette*.

Physicians are wont to look for all the influences exerted to the bromine rather than to the base, and yet when full doses of any one of the potassium salts are used a definite and well-marked physiological action takes place in addition to that produced by the bromine, iodine, or other medicament ingested with the potassium; further, the effect of the potassium in large amount is distinctly

poisonous to all protoplasm, and in small doses it acts as a depressant to important vital functions, and for this reason preparations in which sodium is the base are to be preferred. With these views, however, some of those present when Dr. Mitchell read his paper did not agree, and Dr. Dana, of New York, went so far as to speak of the possibility of potassium exercising any depressant effect as a "bugaboo" unworthy of credence and never seen in practice, although the writer of this article asserted that he and other clinicians had noted this well-known fact by the bedside.

If we regard the matter from a purely scientific basis, we find that as long ago as 1867 Rabuteau, from his investigations, laid down the rule that the poisonous action of the metals increased with the atomic weight amongst the elements of the same group, so that potassium, the atomic weight of which is 39, is more poisonous than sodium, the atomic weight of which is 23. Again, if we take chlorine compounds, we find that chloride of potassium is a muscle-poison, and that chloride of sodium is innocuous. The studies of Guttman, Ringer, Claude Bernard, and several others, prove that "potash salts are all far more poisonous than soda salts," and that the acid of the salt plays no part in producing the poisonous symptoms in such salts as the nitrate, carbonate, and chloride; or, in other words, potassium is always a poison in itself. Full doses of the potassium salts, we are told by Ringer, lessen the frequency and force of the heart's beats and make them irregular; and again, "that soda salts in twice or three times the quantity which proves fatal in the case of potash salts, produce no effect on the system save a passing weakness.' Even in still larger doses soda salts exert no influence on the heart or the temperature, or on the brain, cord, nerves, or muscles, whereas potassium does depress all these functions or parts. In regard to bromide of potassium, Ringer states, after discussing the experimental evidence, "it produces the same symptoms, in the same order, as other potash salts, and that the more or less rapid induction of these symptoms depends on the amount of potash the salt contains. Bromide of potassium, like the chloride, paralyzes not only the central nervous system, but likewise the nerves, muscles, and heart, sooner than the nerves, and the nerves sooner than the muscles; and, therefore, we conclude that these effects of bromide of potassium, which it possesses in common with all potash

salts, are due solely to the potash, the bromine playing no part in the process."

Leaving the scientific side of the question, and turning to that of practical therapeutics, we need only reiterate the fact that we have seen potassium salts in full doses produce depression, and quote from the New Sydenham Society's translation of the *Lectures on Pharmacology*, of Professor Binz, of Bonn. Thus, after detailing the symptoms produced by large doses of bromide of potassium in healthy young men, in whom there were a fall of temperature and feebleness of the heart, Binz says:

"Control-experiments with potassium chloride showed that the effect on the heart was always largely due to the potassium. Later on we shall have yet to consider in detail the very marked effects which the salts of potassium exert upon the heart's action."

And again Binz states:

"Sodium bromide, taken by the same individuals in the same manner as the potassium salt, produced the same effects on the nervous system, but not on the pulse and temperature."

To quote once more from Binz:

"If potassium bromide has been taken for a considerable time, or even for a few days only, by susceptible persons, it has been observed to affect the *heart* unpleasantly, the pulse becoming feeble, irregular, and intermittent. This is doubtless due to the potassium, which, constituting 33 per cent. of the salt, may very readily, given in the large doses above mentioned and in a form so easily absorbable, exert its depressing influence upon the heart's action. *For this reason sodium bromide is preferred by many physicians.*"

Recently we are told in the London *Lancet* of April 4, 1896, that

"The coroner for Mid-Essex held an inquest on March 26th on the body of a man whose death appears to have been due to excessive indulgence in what is usually considered to be a comparatively safe drug—namely, bromide of potassium. Suffering from neuralgia, he had been in the habit of taking this salt in doses of two to three drachms. The drug does not appear to have produced any of the usual symptoms of bromism, but may have caused the palpitation of the heart of which the deceased had frequently complained. During the night of March 23d he felt very cold, gave two deep gasps, and almost immediately expired. The medical practitioner who was sent for stated at the inquest that he found the deceased quite dead, his mouth wide open, the eyes half closed, and the pupils somewhat dilated. A bottle containing the drug was on the table, and examination showed that it was pure bromide of potassium. The witness attributed death to failure of the heart's

action, caused by taking the bromide. This case is interesting for several reasons. It proves in a marked manner the danger of taking any drug, however harmless it may be reputed to be, in large and repeated doses without the advice of a medical man. No doubt in this instance a medical attendant would have recognized the depressant action the salt was exerting upon the heart and would have discontinued its use. Even in the most modern works on therapeutics this danger is not mentioned, yet it is well known that all potassium salts cause 'depression, shown by diminished energy of contraction of the cardiac muscle, with final stoppage in diastole' (T. Lauder Brunton). As this bromide is constantly administered in large and repeated doses, the action of its basic constituent should always be borne in mind, and if signs of its depressant effect are observed its use should be abandoned, the bromide of some other base being selected if in other respects the action is beneficial. Many secret remedies for 'fits' contain this drug in large quantities, and it is evidently desirable that the public should be warned that their use is not unattended with danger."

We may conclude, therefore, that the bromides are not as harmless drugs as some have thought, and in some cases they are capable of producing maniacal delirium, whether the patient be sane or insane.

Finally, if they are used, the sodium preparations are to be preferred to those of potassium.

DISCUSSION.

DR. H. C. WOOD: It seems to me probable that the statements that the bromides produce maniacal delirium are chiefly due to incorrect reasoning on the part of the observer. The suppression of the epileptic fit by the bromide may be followed by maniacal outbursts, which are, however, not directly produced by the bromide, but are really epileptic nerve-storms. In other words, in such a case the bromide has not influenced the cerebrum to produce mania, but has simply changed the channel of the epileptic discharge; so that, instead of a motor paroxysm, there is a maniacal delirium. I am sure, also, that a potassium salt produces a potassium effect; and that, therefore, when large doses of the potassium bromide are given, mingled with the effects of the bromine are those of the great amount of potash in the system. As the result of large experience, extending over years and hundreds of cases, I am sure that the ammonium salt is superior in epilepsy to the potassium salt, and that the best effects are to be obtained by a combination of the ammonium and strontium bromides, usually two or three parts of the first to one or two of the second; the strontium salt having a distinct influence in preventing digestive disturbance.

DR. I. E. ATKINSON: The use of bromides in the treatment of nervous disorders is so widespread and so universal that if such dangerous effects were part of their ordinary action the observation would be much more common. The results spoken of by Dr. Hare may be possibly looked upon as the direct result of the changes in the character of the disease. Another point to be remembered in considering the effects of bromides is the idiosyncrasy of the patients. All drugs will produce untoward effects in certain individuals, and we must recognize these results as manifestations of individual idiosyncrasy.

DR. HARE, in closing the discussion, said: That there is a widespread belief in the untoward effects of the bromides is shown by the fact that nearly every one of the asylum superintendents who has written to me on the subject ends his letter by saying that he hopes I will succeed in impressing the general practitioner with the fact that he should not give bromides. The first thing to be done when a patient is admitted to an asylum is to build up his system and cut out the bromides altogether from the treatment. I do not think the untoward effects are due solely to the use of bromide of potassium, but that the general depression of the health, due to the use of bromides, tends to increase the mental unbalance.

REFLEX NEUROSES CONNECTED WITH THE ABDOMEN.

By NORMAN BRIDGE, M.D.,
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A FEW reflex nervous symptoms of abdominal disorders, and abdominal reflexes of other disorders, are so common as instantly to illustrate the possibility of such phenomena. Headache of various kinds, especially migraine, aberration of vision, palpitation and irregular action of the heart, and paroxysms of asthma, all due frequently to some disorder or irritation of the stomach, are of common occurrence. There are several other varieties of reflex symptoms caused by gastric derangements, and others due to disorders and worriments of the intestines, kidneys, uterus, ovaries, and other abdominal organs that are less common, and are extremely varied in character. The fact that many of them are little understood and rarely appreciated is justification of any attempt to study them comprehensively.

Some of the reflexes are chiefly significant by the annoyance they give the patient; all are liable to be confusing in diagnosis; some are the source of intense suffering; while a few of them are capable of simulating grave and even mortal organic diseases, and may probably continue with varying and fluctuating severity for months or years.

A common reflex phenomenon is sudden and pronounced peristalsis of the intestines soon after the ingestion of food, leading to the free discharge of gas or of a diarrhœal passage or two. This occurrence leads the cruder lay minds to suppose that the food passes through the alimentary canal in the ten minutes following the meal, and constitutes the particular passage, a thing that may be possible but practically does not happen. This form of diarrhœa is frequent; but it is, of course, the food of previous meals that is expelled from the bowels, whatever may be the explanation of it; undigested and identifiable

articles of the meal just devoured are never passed. It is a case of food introduced into one extremity of the digestive tube causing excrement to be discharged from the opposite one. But, of course, it cannot occur under normal conditions of physiological balance; either there is some actual irritation of the mucous membrane of the colon (for the diarrhœa usually concerns that portion of the canal only) or great irritability of the nerves of the part. Reasonably the former most obtains, and is dependent on intestinal, often consecutive to gastric, indigestion, decomposing food (decomposing in the sense of being chemically changed by unphysiological processes) irritating the intestinal lining and inducing a discharge of serum and mucus which make the passages diarrhœal in character. But given the irritation of the colon and its abnormal fecal matter, we have yet to find an explanation of the occurrence of the dejections so quickly and regularly following each meal, the sequence continuing sometimes for many successive days. Reduction of vitality of nerve-centres by extreme loss of blood sometimes causes spasmodic muscular action. The blood-supply of the colon is slightly reduced by the physiological congestion of the stomach after a meal. Is this sufficient to explain the intolerance of the colon at the moment? Or is it due rather and more to a theft of nerve-force from the colon by the stomach? Anyway the diarrhœa is a reflex one; the event is suddenly provoked by the introduction of food, sometimes even by water, into the stomach.

The same sort of phenomenon is produced in some sensitive natures by the emotions of embarrassment, diffidence, apprehension, and fear. Thus many public speakers are annoyed by a desire to go to stool just before rising to address an audience, and there is a record that one preacher was obliged to give up his profession on this account. The phenomenon in such cases is reflex, although the exciting cause has an extra-abdominal source.

An analogous form of reflex is the formation of gas in the intestines soon after the eating of a meal, especially if the latter is rather large in amount or includes food either unwelcome to the stomach or difficult of digestion; and the explanation of it, its pathology, is probably similar to that of the diarrhœa already referred to. The gas is usually without fecal odor, and the rumbling begins often very soon after eating; at times, however, it is postponed for a variable period extending to the limit of an hour. One patient, a middle-aged man

in fair health, was in the habit of eating for his Sunday evening meal a bread and butter sandwich with a glass of milk, and invariably had, beginning within two hours, an accumulation of odorless intestinal gas which would continue to be voided for hours, often making his sleep much troubled. On week-day evenings he was wont to eat a light meal with weak tea or some other hot drink, and rarely was troubled with flatulence.

Another patient was a man about forty years of age, a rather nervous person, and working hard at a business full of annoying details. One winter he became much debilitated and very nervous, and was obliged to go away for rest and recuperation. One of his most annoying symptoms was almost constant borborygmi for a number of hours after taking even the lightest meal. There was neither diarrhœa nor constipation; the gas seemed to be forced through a length of the intestine, to meet some obstacle in the shape of a spasm of the tube, and then rush back on the cessation of the peristalsis.

Gas forms or accumulates in the intestines (the small one, probably) in many cases of nervous women with more or less uterine or ovarian irritation, often accompanied by pain in the top of the head. The gas is not voided, a fact that points to its restriction to the small intestine, and always appears most in the after-part of the day. The pathology is probably a slight reflex paresis of the intestinal walls that allows the gas to accumulate. But the development of the gas is sometimes so rapid as to warrant the theory of its secretion by the mucous membrane. Mental excitement may cause similar gas development in very susceptible women. From embarrassment, fright or chagrin, the abdomen may suddenly swell up, the clothing becoming tight and breathing disturbed by elevation of the diaphragm, and marked tympanites occur without the expulsion from the bowels of a particle of gas.

Of the dragging backaches (without tenderness to touch or motion) that are relieved by horizontal posture, the most prolific cause next to varicocele and uterine disease is some irritation of the stomach and bowels. With the backache there may be no discomfort in the alimentary tract itself, but the two phenomena may be interchangeable; with intestinal discomfort, diarrhœa, heartburn or weight in the stomach, no backache; and *vice versa*. This form of backache is sometimes induced in sensitive persons by a cathartic, especially if it

contains calomel; and intestinal catarrh—which means catarrh of the colon—occasionally produces it also.

Another and quite different sort of reflex pain, but clearly connected with intestinal indigestion and irritation, and sometimes with the migraine habit (itself aggravated by abdominal—*i. e.*, digestive—disturbances), is a slight, dull, fluctuating pain in both sciatic nerves, without tenderness or pain on motion, and lasting to the limit of a day. One patient had this phenomenon to a marked degree, and it always disappeared the instant the intestine was freely evacuated and the conscious irritation of this organ was over. Dr. Putnam reports a case[1] of a middle-aged man "who has had migraine since childhood and belongs to a neurotic family." He suffered at times, aggravated by exertion, "from violent pain in both thighs, which comes on very gradually, beginning at the knees and spreading upward, eventually passing away after a night's rest." Putnam evidently regarded the symptoms as related to the migraine or as reflex and not an ordinary neuralgia.

A form of abdominal neurosis less understood is the vague discomfort, difficult to describe, a pain sometimes, although usually not, seizing the lower extremities (mostly the legs), occurring often in children and in the young, and then usually called in America "growing pains," inducing wiggling of the legs and feet, great restlessness and frequent outcries. Irritation of the stomach or bowels in some sort is usually the cause, a loaded colon being the most common, but stomach overloading or worry may easily cause it also. A child going to bed with a light supper is less likely to be troubled in the night with the "pains." If the latter come on, however, a free evacuation of the colon by an enema or a glycerin suppository is likely to lessen or stop the suffering. And some adult patients nearly always have, simultaneously with the leg symptoms, or coming on some time after they begin, flatulence, with expulsions of gas, indicating that the colon ought to be evacuated.

In some cases it is a matter of experience that the leg symptoms never come on from eating a large meal or one of any particular kind of food, provided the colon has just been freely evacuated, showing that probably the symptoms are reflex and produced by irritation of

[1] A System of Practical Medicine, etc., vol. v. 1240.

the nerves of the intestine. The part the stomach probably plays in such cases is to worry the intestine, as it does in the attacks of flatulence and diarrhœa already referred to.

Another form of reflex neurose is prurigo of the legs and pudendal regions that at irregular times and intervals seizes a patient with great suddenness and often with harrowing severity, and lasts for a few minutes at a time. It recurs again and again while the cause continues, and in its severest form will quite unnerve the strongest man unless he is permitted to rub, scratch, or soothe the suffering spot. The cause is usually a loaded or slightly irritated colon, with the addition of some inscrutable nervous element that is only occasionally present, for a loaded colon will not always produce it; but the complete evacuation of this canal nearly always results in the prompt relief of the itching. The pathology of the disorder seems to be similar to that of the leg symptoms and the flatulence already referred to, and both these are sometimes convertible or interchangeable with it in the same individual.

One patient, a boy of active pursuits and habits and a hasty and hearty eater, had such pruritus and tingling of the scrotum and pubic region as to nearly drive him to frenzy. The sensation in an intense degree would seize him suddenly, and he would rush unceremoniously from the table, from a company, or from his work, to a place of seclusion where he could scratch and almost tear himself. A free evacuation of the bowels would promptly put an end to it, and his experience soon taught him this, and he would seek relief in that way. In this patient extreme flatulence and the pruritus sometimes alternated from the same cause.

A man of upward of forty years, with some grave abdominal disease of doubtful diagnosis and with marked indigestion, constipation, and flatulence, had much of the time most annoying numbness and tingling of the hands and feet. But this symptom would promptly grow less or disappear on a free evacuation of the bowels, and the taking of a few meals of digestible food that was digested. This patient had also a profound sensation of prostration after a specially indigestible meal—the instant the meal was disposed of the prostration was gone.

A phase of reflex quite analogous to the one just described is the common hives or urticaria, from gastric irritation. This is usually

produced by some article of food that from the personal idiosyncrasy is poisonous, as fish, shell-fish in some peculiar condition, or strawberries; yet it may be induced by an irritated condition of the stomach, even when empty of food, and probably by irritation of the intestines also. And while irritation of the skin and vicissitudes of temperature may precipitate and even cause an urticaria, the reflex pathology of this affection is too well proven to need discussion. There is no question in my mind that many paroxysms of *asthma* due to overloading of the stomach are similar in pathology to the urticaria. That is, a swelling of the bronchial mucous membrane, not unlike that of the skin in hives, occurs as a reflex effect of the gastric irritation, and produces the asthma. Whether this is the mechanism of these attacks or not, it is certain that many paroxysms of asthma are reflex and due to irritation of some of the abdominal organs, especially the stomach.

Perhaps the reflex asthma is due, sometimes at least, to narrowing of the bronchi by muscular spasm of their walls. This is a current theory, and has one justification in still another reflex neurose—namely, that of spasm of the glottis in many cases of laryngismus stridulus, occurring especially in children. This is an ideal example of the reflex mechanism, and is demonstrated sufficiently by cases where the spasm vanishes on the occurrence of free emesis, whether spontaneous or induced by drugs or otherwise.

Most important of all, there is a class of cases of paroxysmal severe pain, often of the most excruciating character, that one seems forced to regard as in some way connected with slight disorders of the intestine or other abdominal organ, as, in fact, pure reflex pains, at least in their beginning.

The pain in some of the cases is located in the perineum, or in the neighborhood of the urethra, if not in it; sometimes in or about the rectum, and without a particle of tenderness in these organs or any of them. The paroxysms may occur from once in a day or two to many times a day, and last from five minutes to an hour. At times a paroxysm is coincidental with the act of urination, less often, but occasionally with that of defecation. Sometimes a lesion, catarrhal in character, is to be demonstrated in the lower colon or bladder, but sometimes for months nothing of the sort shows itself. The pain is so severe as to suggest a grave, even malignant disease, but time

fails to demonstrate it, the patients recovering after a few months, or going on for years with only slight improvement, but without that cachexia that belongs to malignancy. Cases I. and II. (heretofore reported in the *Southern California Practitioner*) illustrate this form.

A man of forty years had intestinal indigestion for a year or more, which developed a catarrh of the descending colon and rectum. Finally attacks of intense pain occurred in the deep perineum, which the patient located in the neck of the bladder. They occurred every day for a month, and disappeared on the improvement in the general health. The attacks would only last for a few minutes; occurred two or three times in twenty-four hours, and always preceded, by only a few minutes, a discharge from the bowels of fecal matter with mucus and occasionally with a particle of blood. Urine was frequently voided after the paroxysm, but not always, and the pain seemed to have no necessary connection with urination.

CASE I.—Mrs. L., aged sixty years, mother of three children, had been for several years a dyspeptic of a mild type. Paroxysms of intense pain came on suddenly, apparently without cause, and were repeated once or more times daily for many weeks, with often more or less continuous pain in the intervals. The location of the pain was in the rectum, vulva, urethra, vagina, and the body of the perineum; sometimes she would locate the suffering at one of these points, sometimes at another; at still other times she would say the pain was diffused over a considerable area in the region named. In character the suffering was a sudden seizure of intense pain, which would last from several minutes to an hour or more, when it would pass off slowly, often leaving a sore, slightly painful feeling; yet there was never any tenderness except during the paroxysm, and very little then. An evacuation of the rectum or bladder would at times seem to provoke a seizure, at others it had no effect.

Repeated careful manual examinations failed to reveal any, even trifling lesion to account for the case. Examination of the urine was negative. The trouble was aggravated by overeating, indigestion, constipation, or diarrhœa. Occasionally she passed by the bowels a trifle of bloody mucus. Slight benefit resulted from a strict regimen, gentle laxatives, and mild diuretics. Powerful anodynes were called for at times. There was no fever. Appetite was fair, and there was only slight loss of weight. After two or three months the trouble slowly passed off without further revelation as to the etiology, and the recovery has been permanent for about nine years, during which time the general health has been good.

CASE II.—Mrs. B., aged sixty-five years, the mother of several children, a thin but very healthy person till the beginning of this sickness; found four years ago that pain occurred in the urethra, especially after micturition. It

would last but a minute or two at first, but before long grew worse and lasted longer, and occurred between the acts of urination. The character of the suffering in nearly every particular closely resembled that of Case I.; one of the exceptions was the almost constant location of the pain in the urethra or neck of the bladder. The pain was aggravated by indigestion, by the act of eating, by diarrhœa, by irritation of the bowels, and by any irritation of the bladder. Occasionally, early, there was a mucoid stool with a staining of blood, after which the pain would be worse, and it was suspected that some malignant or other inflammation of the lower part of the colon (there was found no lesion in the rectum) was responsible for the seizures; but months ago this symptom mostly recovered. It has returned from time to time in slighter degree, or, rather, the mucus, not the blood. At times there has been a slight catarrh of the bladder, and medication of it has seemed to help the case, but after it has completely recovered the paroxysms have returned. The vesical catarrh returned again and again, but is now nearly well, although she urinates too frequently. A curious circumstance was that the mucus sometimes came from the bladder in one mass, wholly unmixed with the urine. Several manual examinations made at variable periods during the first year and a half failed to reveal any sufficient explanation of the suffering. It must be said, however, that there was hyperæsthesia of the vagina and urethra, and any examination of these parts caused suffering, which was intense if the vagina was distended at all. There was no disease of the kidneys. An able surgical specialist had her under treatment for several months, but found no occasion for any operation.

Medication had little influence over the case; rest in the horizontal position was beneficial. The patient is now better, but has not recovered; she still has the pain more or less. She has a fair appetite, has never lost much weight, and has now nearly regained all she lost; she has never had fever, and is not cachectic. She declares that there has never been a day for two years when she could eat a large meal without provoking a paroxysm of suffering in the urethra within fifteen minutes; but she has learned that if before a meal she takes a cupful of hot water, with a few drops of essence of peppermint and about ten grains of bicarbonate of sodium, she is much less likely to have a severe paroxysm, but does not escape one entirely. As a result of this gastric sensitiveness, she has for a long time avoided eating large meals, but takes instead five or more small ones a day.

Case III.—Man, about the middle period of life, healthy in the main, has occasional attacks of gastric indigestion and an occasional diarrhœa, lasting a few hours or days. He formerly was a migraine subject. In the last six or eight years he has had, following a diarrhœa in each instance, several attacks of what have appeared to be intense rectal congestion and catarrh. Mucoid passages occur, and the swelling of the mucous membrane of the rectum is so extreme as to give a sense of intense fulness, aggravated at times by pain on sitting down. Great pain is experienced in the transmission through the rectum of fecal matter, and the pain through the mass

when the viscus is quiescent is at times so extreme as to suggest the presence of something more severe than a proctitis. No fever ever occurs. There is little loss of weight or appetite.

After continuing for one to three weeks the trouble may rapidly disappear and not recur for a year perhaps.

No treatment seems to do much good. Perhaps the most useful is an injection of hot water, often repeated. Suppositories of sulphate of codeia and tannin do some good.

CASE IV.—W. Y. S., aged thirty-three years. Never very vigorous. Has had periodical and violent headaches all his life. Formerly the attacks would last one or two days, latterly only one day; formerly they occurred once or twice a week; now they come only once in three or four weeks.

He had some lateral curvature of the spine at twenty years, for which he wore a brace three years. After that he was in good health, except for occasional headaches, till within five years.

Five years ago he began to have stomach trouble, and the headaches grew worse. Later he would have attacks of abdominal pain, a coated tongue and diarrhœa; during many months past the attacks have occurred as often as once a month, and lasted three or four days. With the diarrhœa there is tenesmus and latterly passages of blood. With the attacks of diarrhœa the headaches have decreased, and he has reached the conclusion that the former were nervous in character, and somehow took the place of the headache, which is probably true.

He has various other nervous symptoms. With the worst attacks of diarrhœa he has palpitation; occasionally stiffness of joints appears temporarily, for which he has taken salol; has had for several years an area of numbness on the outer aspect of the left thigh; at times cannot think or write or look, the tight feeling in the head is so severe; if he lies upon a hard pillow, he is sure to have pain in the neck.

Malignant diseases of the bladder or urethra, or of the rectum or sigmoid flexure of the colon, are usually attended with more or less severe suffering. As these organs are viscera of the body for the accumulation of excrementitious substances that must be evacuated at intervals by complicated muscular movements, it is rational to see in these acts cause for paroxysms of pain. All lesions that involve muscular tissue must cause pain at the time of its contraction. Of course, severe irritation or inflammatory lesions of any of the organs of the abdomen may cause pain of various degrees of severity and of variable character. Malignant disease of any of the organs of the abdomen may cause frequent, paroxysmal, and at times nearly steady pain.

Chemical and germ poisons in the blood, by affecting the ganglionic centres or nerves, frequently cause severe pain in the abdomen, as of

other parts; for example, lead and malaria. Neuritis of some of the abdominal nerves is not an irrational explanation of some cases of very persistent pain. Tabes may cause a form of abdominal pain.

One of the severest forms of pain is that known as reflex; that which is due to irritation of some organ distant from the seat of pain. Headache due to indigestion is one of the most marked examples, while migraine is a periodical severe pain due either to some undiscovered reflex irritation or to some cerebral or nervous defect that exposes the parts to periodical suffering from the effect of the normal environment and vicissitudes of life.

The intimate relation of the digestive organs and the function of digestion with migraines shows the vulnerability of the abdominal nerves to disturbance of function and sensation without any structural disease. The nerves of the abdomen (other than the pneumogastric) are more or less involved in the migraine phenomena, as shown in the digestive disturbances of this disease, the vomiting and diarrhœa that accompany or follow the seizures, and in the various erratic sensations and experiences of the abdomen that are convertible with the attacks of pain. An ideal migraine may become a recurring diarrhœa or muscular neuralgia, or prolonged spasm not unlike that of hysteria, which may last for months. Or a migraine occurring for years with marked regularity, and with no visual disturbance whatever, may gradually change, as it did in one of my patients, the pain being omitted entirely and the most marked eye disturbances of migraine, and sometimes with vertigo, taking its place.

In the cases related above the pain and dysæsthesiæ would seem to have been caused by different influences. In the case of the boy with pruritus the cause of the itching and tingling must have been a reflex one in some worriment of the intestine due to constipation, or to the absorption of some ptomaïne from the mucous membrane, which the free catharsis stopped. In Case III the rectal congestion was most undoubtedly due to the influence that earlier in the life of the patient caused the migraine. It is one of the many possibilities of this diathesis. Case IV illustrates this in a marked manner. As to Case II we should perhaps speak with less positiveness, since the patient has not yet recovered, and neuritis may now exist; but Case I recovered completely, so the cause of the pain must have been some reflex irritation, probably in the large intestine.

True convulsions from gastric and intestinal irritation are a marked example of reflex action. Indigestible and undigested substances in the intestines of children often cause convulsions, even where the patients have no marked tendency to epilepsy; tape-worm occasionally has the same effect. One bottle-fed baby had several convulsions, each of which was immediately consecutive to a slight change of the food.

Vomiting is a reflex act, and is caused by numerous and diversified influences. Injury of the stomach by irritating contents is the most rationally acting cause. Mental impressions, disagreeable sights and odors often produce it. The vomiting of pregnancy is a reflex act; so is that of acute appendicitis; of spasm and gallstone irritation of the cystic duct in cases of so-called gastralgia without disorder of the stomach, and of renal colic.

Other neuroses having their cause in some state of the abdominal organs are reflex inhibitions of function of various distant parts of the body. Probably the intestinal canal and the uterus are more responsible for such phenomena than any other organs, and some curious, even grotesque instances of inhibitory action have been recorded, mostly involving muscular parts. The very irritation of hepatic colic, of renal colic, and of acute appendicitis that causes reflex vomiting may, if severe enough, induce for a time a complete inhibition of intestinal peristalsis, so that powerful cathartics are quite inert.

CASE V.—The author has reported elsewhere (*Chicago Medical Journal*, July, 1874) the case of a boy of fifteen years, who, a week before consulting him, had for the first time in his life been noticed to stammer slightly. He also had a slight pain in the breast and head on trying to speak. The stammering grew worse, and in five days was so bad that he could only speak with great suffering. For two days he had been obliged to write his communications, not speaking at all. He had fallen into a fit when his father tried to compel him to speak. On insisting at the consultation that he should answer a question, "he put his hand to his head, seemed in great agony, and half cried, while in a hitching, stammering way and with great effort" he blurted out a monosyllable. There was no aphasia, and he spoke his word distinctly. Once during the week he had for a moment spoken easily and distinctly on awakening from sleep, and once on becoming angry. No evidence of bodily disorder could be discovered, except severe constipation, which had come on shortly before the attack. At the time of his visit his bowels had not moved for four or five days. The symptoms disappeared promptly on free catharsis from rhubarb and calomel. The boy returned in five days, and could speak normally and was well.

CASE VI.—Miss K., school teacher, aged thirty years, a fairly vigorous woman, had a uterine fibroid the size of a large fist, which caused her little annoyance except at menstrual times and when she was overworked and run down in strength; then she would lose her voice suddenly, and be unable to utter a vocal tone for a variable period from a day to a month, with this exception, that on a moving street- or steam-car she could speak aloud and normally. The instant the car would stop her voice was gone, frequently in the midst of a word; its first part would be spoken aloud, the last in a whisper. Stopping at a railroad crossing to let a train pass her, she found her voice, to lose it again the instant the rumbling sound and jarring sensation were gone. No treatment or coaxing or goading[1] of her vocal apparatus had the slightest effect to make her speak. She was a woman without a single apparent general symptom of the hysterical temperament.

CASE VII.[2]—Dr. Hammond relates the case of a girl, aged twelve years, who had a suddenly developed paraplegia. He gave several doses of castor oil and santonine, with the effect of discharging from the bowels a number of round worms. The paraplegia disappeared "in the night."

One of the most marked reflex inhibitory effects is insomnia due to a loaded or irritated colon. This phenomenon has been demonstrated by many sleepless mortals. They can sleep if the canal has been recently evacuated; if it contains even a trifle of fecal matter, they sleep little or none. Absorption of ptomaïnes from the intestines might produce insomnia, but in these cases that cannot be the chief cause, for the tranquillity and somnolence follow too promptly upon a colon flushing; moreover, other intestinal irritants beside decomposing fecal matter may induce insomnia.

A secret treatment for insomnia has been exploited with much declared and some real success, and consists in nothing but a large enema taken just before bedtime. It is a good treatment, especially if the normal salt[3] solution is used for the flushing.

[1] The treatment by electrical shock was not tried in this case.

[2] Fagge, vol. i. p. 407.

[3] Six parts of chloride of sodium to 1000 parts of water. This is approximately represented by a heaped teaspoonful to the quart.

TREATMENT OF LITHÆMIA.

By B. K. RACHFORD, M.D.,
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Lithæmia is a term introduced by Murchison to designate a large group of symptoms which he thought to be due to an excess of uric acid in the blood. The term uricæmia had previously been used by the elder Flint for the same porpose, and under the term lithuria a number of recent writers have grouped the same set of symptoms. "Concealed gout" and "American gout" have also been very largely used in naming these same clinical manifestations. The writer has contributed a number of papers on this same subject under the term "leukomain poisoning." All of these terms have come into general use, and all of them are more or less inaccurate. The term lithæmia has been selected to head this paper not because of its propriety, but because of its long and widespread use by medical writers. Lithæmia comprehends all of the manifestations resulting from the presence of the alloxuric bodies in the body media. Uric or lithic acid is one of these alloxuric bodies. It may, in fact, be considered as the representative body of its class, even though it plays a comparatively insignificant *rôle* in producing the symptoms of lithæmia. Under the above definition it is evident that the symptomatology of this condition will be very complex. It will include the symptoms which are thought to be due to an excess of uric acid in the urinary passages, and it will also include a large group of nervous symptoms, such as migraine, migrainous epilepsy, and certain gastric neuroses which the writer believes to be due to an auto-intoxication caused in great part by the xanthin bodies. Besides these there are many other symptoms with which every practitioner is familiar, but which I cannot here give space to name. I will, therefore, at once pass to my theme—the treatment of lithæmia.

The dietetic treatment of lithæmia is of the first importance in

infancy, as it is at all periods of life. Mother's milk is an ideal food for lithæmic infants; but when it becomes necessary to supplement this food it is best to do so with cow's milk to which cereals have been added. I have been much impressed with the importance of adding barley or rice-water to cow's milk as a food for these children. Jacobi for many years has enthusiastically advised that cow's milk as a food for infants should always be mixed with cereals, and it is my experience that this admixture with cereals is of special importance to lithæmic infants. Beef-juice and meat-soups and teas should not be given to lithæmic infants or children. They are at all times contraindicated. When the lithæmic infant becomes a child the milk and cereals, including bread, should continue to occupy the most important place upon his bill of fare. Milk and cereals are, in fact, ideal foods for lithæmics of all ages. As the child develops it becomes necessary to add eggs, fish, and poultry to his diet. These foods are very much to be preferred to butcher's meat as a means of furnishing proteid food to the rapidly developing lithæmic child. Butcher's meat may, however, be allowed in small quantities once a day to lithæmic children who lead an active outdoor life. In advising as to the proscribed and prescribed proteid food for lithæmic children it is well to keep in mind that the following foods are to be recommended in the order named: milk, eggs, fish, oysters, poultry, game, and butcher's meat. At the beginning of this list we have the best, and at the end the worst foods for lithæmics of all ages. Lithæmic children should be taught early to eat vegetables and fresh fruits. In fact, vegetables and fruits should be the basis of the diet of lithæmics at all times and at all ages. Fresh fruits and fresh vegetables should enter largely into the diet of all lithæmic children, and these foods together with milk, eggs, and cereals, should constitute the almost exclusive diet of these children until they are old enough to live a very active outdoor life. Then, as above indicated, fish, poultry, and in small quantities butcher's meat may be added to the diet.

In the treatment of adults I advise that they eat moderately of simple food and abstain absolutely from wine and malt liquors. In this bit of advice we have a condensed statement of the dietetic management of lithæmia. Overeating is a factor in its cause, and undereating is a factor in its cure. Lithæmics for this reason should be

advised against taking an excess of food of any kind. Meats may be taken only in such quantities as are necessary to supply the proteid waste and repair of the body, but it will be found that most lithæmics take meat largely in excess of this quantity. It will, therefore, be necessary to place restrictions on the quantity of meat taken, and substitute for the meat poultry, game, fish, oysters, and eggs, as above directed. No harm, however, can come to lithæmics, leading an active life, from the moderate use of these simple proteid foods. The only care necessary is to avoid an excess of these foods, and to see that they are prepared in a simple and digestible form.

Fries and salads are objectionable, and fresh pork, lobsters, and crabs are not to be commended. Sweets, such as candies, pastries, and preserves, are to be used sparingly, if at all. The knowledge that sweets are injurious to lithæmics is a bit of information borne of clinical experience upon which almost all writers are agreed. Sweets are, therefore, to be restricted, even though we cannot trace the connection between this class of foods and the nitrogenous poisons which are thought to be the cause of the symptoms of lithæmia. Milk, cereals, fresh fruit and fresh vegetables should continue to be the most important foods of lithæmics throughout life. At the two extremes of life they should constitute almost the exclusive diet of these patients, but during late childhood and early adult life, this being the period of growth and greatest activity, it is necessary to supplement this diet with proteid foods as above directed.

Exercise in the open air is scarcely less important than diet to lithæmic children. They should, therefore, be encouraged in all kinds of outdoor athletic sports. It will be found that many of these lithæmic children require a great deal of urging and commanding in order to have them take the proper amount of exercise in the open air. It is a common observation that lithæmic children are averse to outdoor exercise and very fond of indoor intellectual pursuits. The out-of-school companions of lithæmic children should be bicycles, skates, and tennis racquets instead of books. Wholesome exercise in the open air is necessary to the proper physical and intellectual development of any child, but lack of exercise is especially baneful to one of inborn lithæmic tendencies. Exercise promotes nitrogenous metabolism by furnishing the conditions for the more complete oxidation of the alloxuric bodies into harmless

nitrogenous extractives. The air in which the exercise is taken should be as pure as possible. City children of this type should have two or three months of active outdoor life in the country every year. They may be sent to the seashore, the mountains, or a neighboring farm, with almost equal advantage. Fothergill believed that a certain amount of pure country air was absolutely necessary to the satisfactory development of lithæmic children.

Before beginning the medical treatment of lithæmia one should make a careful search for such reflex factors as may possibly contribute toward precipitating lithæmic paroxysms. If eye-strain exists, it should be corrected. If pelvic or rectal disease be present, it should be treated. In short, all reflex factors should, if possible, be removed before other treatment is commenced. While I am convinced that the reflex factors have had undue prominence given them in the study and treatment of lithæmic paroxysms, yet I am not pessimistic enough to believe that they should be disregarded in the treatment of these conditions. Pelvic disease, I think, especially demands treatment when it occurs in cases where the lithæmic paroxysms coincide with the menstrual period. The failure of medicinal and dietetic treatment to cure certain lithæmic paroxysms may sometimes be due to the fact that there is present some eye, preputial, or pelvic disease, which continues to act as a potent reflex factor in calling forth these paroxysms. The fact should also be noted that many of these lithæmic conditions yield to treatment notwithstanding the existence of potent reflex factors which yet remain untreated.

The medical treatment of lithæmia should aim to cure constipation and to favor the elimination and promote the oxidation of the alloxuric bodies which are believed to be the *materies morbi* of this affection. The medicinal treatment of this condition, especially in infants and children, may advantageously be begun with small doses of calomel and soda, repeated at short intervals until catharsis begins. After a day or two of rest from medication our little patients may then be given some form of eliminative treatment. Volumes have been written on the treatment of lithæmia by drugs which are given for the purpose of eliminating the poisons of this disease, and there always has been and possibly will be for some time to come, much confusion on the comparative value of these drugs. Carefully formed

individual opinions will, therefore, continue to be of much value in clearing up the medical treatment of lithæmia. It is my belief that the salts of salicylic acid are the most valuable eliminative medicines we have. After the preliminary calomel treatment, it is my custom to place the child on some sort of salicylate treatment. The exact nature of this treatment will depend upon the age of the child and the nature of the lithæmic manifestations. Salol is an especially valuable remedy in infantile lithæmia. I have seen lithæmic infants suffering from chronic intestinal fermentation with gastric crises very much benefited by giving one grain of salol after each nursing. Other intestinal antiseptics will not obtain the same results in these cases, and it is not, therefore, simply a question of intestinal antiseptics. The salol in these cases must be continued for weeks or months in doses to suit the age of the child. If the lithæmic manifestations be an eczema, salol is equally advantageous. To these infants I also commonly give a few grains of phosphate of soda or benzoate of lithia dissolved in the milk of their nursing-bottle. An infant two years of age may be given in this way twenty grains of the phosphate of soda and three grains of the benzoate of lithia in twenty-four hours. The three drugs mentioned—salol, phosphate of soda, and benzoate of lithia—are the ones commonly relied upon in the treatment of infantile lithæmia, and with them great good can be accomplished if they be intelligently used in connection with such other dietetic, hygienic, or local treatment as the special lithæmic manifestation may suggest. Should the phosphate of soda not answer the purpose as a laxative (all of these cases are constipated), it then becomes absolutely necessary to supplement this treatment with a laxative which will evacuate the upper bowel. Enemas and suppositories are not to be depended upon for this purpose. They may be used as an assistance to other laxative treatment, but they are not to be relied upon exclusively. I wish here to especially insist that this laxative treatment is as absolutely necessary to the success of the treatment in the lithæmia of infants and children as it is in adults.

Salicylate of soda may be given, instead of salol, to children after they are five or six years of age. The salicylate of soda made from wintergreen is preferable because it is more palatable and less irritating to the gastric mucous membrane. It should, if possible, be

given in a little seltzer-water, which may, for convenience in using, be obtained in a siphon. The siphon of seltzer may be kept in a cool place, and the seltzer-water may be siphoned into a glass which contains a dose of salicylate of soda. The addition of seltzer water in the way described makes it possible to give salicylate of soda for an indefinite time without disgusting the palate or irritating the stomach. When the child reaches an age that it will take without protest the salicylate of soda in the way described, then it is to be preferred to the salol, but prior to this time the salol is to be used.

But while the salicylates are our best remedies in all forms of lithæmia, the salts of lithium are also of some value in the treatment of certain manifestations of this disease. The natural lithia waters may be used in the treatment of lithæmia, and it is much in their favor that these waters are tasteless and, therefore, readily taken by infants and children. Much of the benefit that comes from the drinking of lithia water is due to the water itself rather than to the lithia it contains. Many lithæmic patients will be found to take small quantities of liquid, and such as these will be greatly benefited by increasing the quantity of liquid taken in twenty-four hours. Mention has previously been made of the importance of giving newly born infants water to drink. In such infants water is often needed to bring in solution and thereby favor the excretion of urates which might otherwise irritate the inflamed urinary passages. For the same reasons lithæmic patients of all ages are benefited by the drinking of water. Much of the benefit that comes to these patients from the drinking of sulphur and other waters at the springs comes from the large quantity of water taken rather than from the medicinal properties of these waters Yet, in giving full credit to water as a remedial agent in the treatment of lithæmia, one must not overlook the fact that many of these waters contain salts that are of real value in the treatment of this condition. Lithia is one of these salts, which has, as I have said, some value. Of the lithia salts, benzoate and the citrate are much to be preferred. I am given to the use of the benzoate almost to the exclusion of all other lithia salts, because I believe I get better results with this salt of lithia than with any other. To young children one may give gr. ss–j three times a day dissolved in milk. To older children it may be given in tablet-form or dissolved in water. The citrate of lithia is some-

what less efficient, but it is more palatable than the benzoate. I have under observation at the present time a lithæmic child now three years of age. She inherits a strong lithæmic tendency, and has had many manifestations of this affection since she was six months old. At intervals of six or eight weeks she will have an attack of painful urination lasting from three to six days. During these attacks the urine is acid and has a heavy deposit of urates. She screams with pain on passing urine during these attacks; she is irritable, fretful, and sometimes slightly feverish. The external genitalia are reddened and inflamed by the passage of urine at these times. These attacks can be relieved and warded off by the lithia waters. During the past year this child has been drinking these waters, and in this time has never had an attack, except when the lithia water was stopped as a matter of experiment.

The soda salts are of great value in the treatment of lithæmia, and the mineral waters which are composed largely of these salts, such, for example, as Carlsbad, have a well-deserved reputation in the treatment of this condition. Phosphate of soda, above mentioned as a valuable salt in the treatment of lithæmia in infants and young children, is of value in the treatment of this condition at any time of life. It has long had the reputation of being one of the best uric acid eliminators. It should be given in large doses of sixty grains to an adult and ten to fifteen grains to an infant three times a day. In infants and young children it can best be given in milk. But phosphate of soda does not, as a rule, in older children and adults produce the cathartic action which is absolutely necessary to the successful treatment of lithæmia. It may for this reason be advantageously combined in the same prescription with sulphate of soda. This will insure sufficient cathartic action. The following prescription has long been a favorite with me in the treatment of lithæmia. I have used this prescription for a number of years as the basis of the medical treatment in almost every case of lithæmia in older children and adults that have come under my observation:

℞.—Sodii salicylatis (from oil of wintergreen) . . ℥ij.
Sodii phosphat. (dry) . . . . . ℥iv.
Sodii sulphat. (dry) . . . . . ℥iss.

M. S.—A teaspoonful, more or less, to be taken in a glass of seltzer water every morning.

I have given this prescription, or a modification of it, for months at a time without producing gastric irritation, and with the most satisfactory results in the relief and cure of lithæmic manifestations. It is very important that dry salts be used in this prescription. The dose is to be regulated by the cathartic effect. Violent daily catharsis is not to be desired, but a decided laxative effect must be produced. It is evident that the amount of sulphate of soda in this prescription may be increased or diminished to suit individual cases. At the present time I am using very largely in my practice the following modifications of the above prescription. It will be seen that these formulæ, given below, combine the drugs which I have noted as being of special value in the treatment of lithæmia:

℞.—Sodii sulphatis, crystals . . . . . 120 grains.
Sodii phosphat., crystals . . . . . 30 grains.
Sodii salicylat. (from wintergreen) . . . 10 grains.
Tincturæ nucis vomicæ . . . . . 3 drops.
Aquæ destil., ... ad ℥iv.
Sig.—Take each morning before breakfast.

℞.—Sodii sulphatis (dry) . . . . . 30 grains.
Sodii salicylatis (from wintergreen) . . 10 grains.
Magnesii sulphas, crystals . . . . 50 grains.
Lithii benzoat. . . . . 5 grains.
Tinct. nucis vomicæ . . . . . 3 drops.
Aquæ destil., ... ad ℥iv.
Sig.—Take each morning before breakfast.

These and other modifications of the prescription above given I have had charged with CO_2 in siphons. In this way I can prescribe the above formula in siphons with the direction to take from one-fourth to one-half a glass of this siphon medicine before getting out of bed each morning. In the beginning of the treatment it is advisable to have the patient take this medicine before getting out of bed. In this way the nausea that sometimes follows the beginning of this treatment is avoided. In the treatment of hundreds of cases of lithæmia I have yet to find a patient, except among young children, who refused to take this medicine. It will agree with any stomach, and may be continued indefinitely without disgust, nausea, or irritation. The dose of this siphon medicine is to be regulated by the age of the patient and the cathartic action produced. It is absolutely necessary to the success of the treatment that a laxative

or slightly cathartic action be produced. This can, as a rule, be effected with the siphon medicine alone, but in some cases when the constipation is troublesome it is advisable to give a mild cathartic at bedtime and follow this with the siphon medicine in the morning. It is better to do this than to give more than one-half a glass of the siphon medicine to produce a cathartic effect. The cathartic taken at bedtime may be cascara sagrada or any simple laxative pill.

In the treatment of lithæmia, it is now, and has been for some time, my custom to give the siphon medicine every morning, for one or two months, and then every other morning, or once or twice a week, as long as I think this treatment should be continued. In connection with the siphon treatment above described I commonly use a one-grain salol-coated pill of permanganate of potassium (made for me by the Upjohn Pill and Granule Company). This pill is to be taken after each meal. The permanganate of potassium is given not only as an intestinal antiseptic, but also because it is a strong oxidizer, and may in this way render innocuous the poisonous uric acid leukomains which have much to do with the production of lithæmic symptoms. However this may be, clinical experience teaches me that permanganate of potash is of value, it matters not what may be the theory of its action. These pills should be salol-coated that they may be non-irritating to the gastric mucous membrane. Such salol-coated pills may be given for an indefinite length of time to patients who have long suffered with irritable and diseased digestive organs. With the above line of treatment I have much success in the treatment of some of the most troublesome forms of lithæmia.

With other types of lithæmia, however, this line of treatment results in only a moderate degree of success. Especially would I call attention to the treatment of migraine by this method There is one type of migraine, as previously noted, in which the severe headache is associated with nausea and vomiting. This type can, as a rule, be entirely relieved by this treatment when combined with the dietetic and hygienic measures previously outlined. I have observed that the more pronounced the gastric symptoms the more amenable these cases are to this treatment. This treatment is, therefore, especially adapted to the relief and sometimes the cure of the severe paroxysmal headaches with nausea and vomiting, and it is

almost of equal value in the treatment of the gastro-enteric type of lithæmia—that is to say, in those cases in which the gastric attacks of pain and vomiting are not associated with headache. I have also seen it act almost as a specific in the nervous dyspepsias of lithæmic origin which are commonly associated with such neurasthenic symptoms as excessive irritability and great depression of spirits.

In brief I may say that one may expect good results to follow this line of treatment in all lithæmic manifestations which are in any way associated with gastro-enteric symptoms. I have patients now under observation who have not had an attack of sick headache in two years, who prior to being placed upon the above treatment had two or three attacks in the month. In a number of these patients, now entirely relieved, the attacks were so severe that morphine hypodermatically was the only drug that gave relief. I am sure that some of these have been saved from the morphine-habit as well as relieved of one of the most distressing ailments. I have also succeeded in curing a number of these cases in which the morphine-habit was firmly established.

Eighteen months ago I was asked to see a boy, twelve years of age, who was suffering frightfully from migrainous attacks. The boy came from a highly intellectual and lithæmic parentage, and from the age of seven he had been having severe periodic headaches, accompanied with nausea and vomiting, and sometimes with gastric pain. His eyes, ears, and throat had been carefully searched in vain for a reflex cause of these headaches. It was in April when I saw the boy for the first time, and learned that he had been having two or three headaches a month all winter. These headaches sometimes confined him to bed for several days, and occurred at such short intervals that he was barely convalescent from one when he was attacked by another. His general condition was also bad; he was pale, thin, and had an anxious look about his face which marked him as a sick boy. I placed him on the above treatment, and he had but one headache in the next twelve months, and that one was shortly after the beginning of the treatment. During the past winter this boy has attended school regularly. He never missed a day on account of sickness. The boy's general health is much improved. Diet and open-air exercise have been valuable adjuncts to the medical treatment in bringing about this very satisfactory result.

This case is but one of many in which I have obtained a like result. The successful cases are by no means confined to children. Adults respond as readily as children to this treatment. One of my most successful cases was the following:

A woman, over sixty years of age, who had suffered from sick headache and other lithæmic manifestations since she was a young girl, I saw for the first time last October. At that time she was suffering from frightful attacks of headache, which confined her to her bed almost half the time. She had been treated by all kinds of specialists in almost all of the larger cities in the East. I placed her under treatment, and from that time to this, a period of nine months, she has had but one severe headache, and her general condition is vastly improved.

There is another form of lithæmic headache which may be designated migrainous neuralgia—that is, not accompanied by nausea or other gastro-enteric symptoms. These headaches are paroxysmal and not infrequently are connected with the menstrual period. Such lithæmic headaches occurring without nausea do not yield readily to the above line of treatment, yet these headaches are also benefited by the siphon medicine, if it be persisted in for a sufficient length of time. But the permanganate of potash pill is, in my experience, of but little value in the treatment of this type of headache. It is in this type of headache that I have derived the greatest benefit from cannabis indica, which I usually give combined with salol, as in the following formula:

℞.—Cannabis indica . . . . . gr. iij.
Salol . . . . . gr. lx.
M. Div. in capsul. no. xii. S.—One after eating.

This prescription may be continued for months at a time if necessary, and is always to be used in connection with the siphon medicine. The cannabis indica and salol capsules may also be used in connection with the siphon medicine in the treatment of lithæmic epilepsy. These most distressing cases are, as a rule, greatly benefited by this treatment. In brief, I may say that the cannabis indica and salol capsules take the place of the permanganate of potash pill in all severe lithæmic paroxysms which are not associated with nausea or vomiting. Where these symptoms exist, as above stated, the permanganate of potash is a valuable aid in the treatment.

In the above outline I have briefly presented a plan of treatment which I have come to look upon as something of real value in the treatment of lithæmia. Yet this outline does not mention all the drugs which are of value in the treatment of this condition. There are, in fact, many other drugs which have found favor in the treat-

ment of this condition. Among such drugs the dilute nitro-muriatic acid and colchicum deserve special mention. Dilute nitro-muriatic acid in five to ten drop doses, well diluted, after meals may be given to older children and adults with decided benefit in the treatment of migraine and other lithæmic paroxysms. Colchicum is also of unquestioned value in the treatment of lithæmic neuralgia. Five to twenty drops of the wine of colchicum taken, well diluted, after meals, will often be found of value in the treatment of painful lithæmic affections. The dose must be regulated to suit the age and idiosyncrasies of the patient.

Only a word will be said concerning the employment of the natural mineral waters in the treatment of lithæmic conditions. For stout and vigorous patients these waters are of great value. The thermo-alkaline springs of Virginia and Arkansas are of special value in the treatment of this type of cases. The waters of the Carlsbad type may also be expected to benefit these patients. The Bedford Springs of Pennsylvania, the Crab Orchard Springs of Kentucky, the St. Clair and Mt. Clemens Springs of Michigan, the Saratoga Springs of New York, and the West Baden and French Lick Springs of Indiana may be recommended to lithæmics.

HEPATIC COMPLICATIONS OF TYPHOID FEVER.

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CONSIDERING the close connection between the liver and the intestines, and the liability of this organ to be involved in ulceration of the bowel, it is surprising that hepatic complications are not more common in typhoid fever. Long series of cases may be treated without a symptom pointing to implication of the liver, or, indeed, without a single sign indicating enlargement of the organ or disturbance of its function. I propose in the following paper to deal somewhat systematically with the complications which arise in the course of enteric fever. The subject has recently attracted a good deal of attention, particularly with reference to the frequency of infection of the bile-passages and its association with gallstones and suppurative cholecystitis. I shall take up the question under the following headings:

I. The focal necroses.
II. Jaundice in the course of the disease.
III. Abscess.
IV. Affections of the bile-passages.

I. FOCAL NECROSES.

A few lines must be devoted to this question, though it has, so far as we know, no clinical significance. The subject has been dealt with quite fully by Dr. Walter Reed, of the United States Army, in a study from the Johns Hopkins Pathological Laboratory, which appeared in the second series in our "Studies in Typhoid Fever," in volume v. of the *Hospital Reports*. These little bodies, known as the lymphoid nodules, were described by Friedreich and E. Wagner, and have since been very carefully studied by a number of

observers. The literature is very fully given in Dr. Reed's paper. Macroscopically they appear as small, grayish, opaque areas, sometimes just on the limit of visibility, at others appearing quite distinctly on the cut surface. Reed states that they cannot always be distinguished with the naked eye. Microscopically the size of these areas varies from a spot involving only a few liver cells, to a region involving the half, or even the whole of a lobule. These nodules represent foci of necrosis of the liver cells. The clumps of typhoid bacilli appear to bear no definite relation to them. Sometimes in the necrotic area there are many polynuclear leucocytes, which almost give the appearance, as Handford states, of a small miliary abscess, or of lymphoid nodules. The foci are subsequently replaced by well-defined areas of connective tissue, which Reed was able to demonstrate in a woman who had died twenty-five years subsequent to the attack of typhoid fever. Necrotic areas can be produced experimentally by the injection of cultures of the typhoid bacillus into the mesenteric vein, and in the human subject they are probably caused by the toxalbumins of the disease, similar to those which develop in diphtheria. So far as we know, these focal necroses cause no symptoms, though it is quite possible that a widespread involvement of the liver lobules might cause an icterus gravis, which occasionally develops in typhoid fever, or, subsequently in their fibrous transformation, lead to cirrhosis.

II. Jaundice.

The extreme rarity of this symptom in typhoid fever may be gathered from the fact that among the first 500 cases forming the basis of this report treated in my wards at the Johns Hopkins Hospital, there was not a single instance.

This has been the experience of most writers on the subject. Murchison, with his enormous experience, states that he "met with jaundice in three cases of enteric fever, all of which were fatal, although in two the jaundice had disappeared before death. In two of the cases there was an autopsy, and in both the liver was small and its secreting cells loaded with oil."[1] Griesinger noted 10 cases among 600 patients with typhoid fever, and Liebermeister 26 in 1420

[1] On Continued Fevers, third edition, p. 565.

cases. These figures are sufficient to show the extreme rarity of this symptom.

The cases of jaundice in typhoid fever may be grouped in four categories: (1) catarrhal; (2) toxic; (3) those associated with abscess; and (4) those associated with gallstones and cholangitis.

It is surprising indeed that catarrhal jaundice does not occur more commonly in this disease. Griesinger states that it is the form which develops early, is quite slight and transitory, and has no influence on the course of the disease. I have never seen an instance at the onset of the fever, but the following is a very good illustration of jaundice at the onset of a relapse, following a protracted attack of nausea and vomiting:

CASE I. *Severe gastric symptoms; jaundice at the onset of a relapse.*—Mr. A., aged about thirty years, seen November 9, 1895, with Dr. Reiche. The patient had been ill for five weeks with typhoid fever of moderate severity. On November 1st, 2d, and 3d the temperature had been normal and the patient seemed to be doing well. The stomach had been quiet, and he had been taking a little extra food. On the 4th, 5th, and 6th he had a little more fever, was restless, had a great deal of nausea, and at intervals vomiting. On the 7th and 8th these symptoms persisted, and on the former date he became jaundiced. He had constant nausea, a great deal of gagging, with the expectoration of much clear liquid, and after taking food he had actual vomiting.

Present condition. The patient looks thin. The skin is jaundiced, the conjunctivæ stained. The tongue is heavily furred and white. He has a small basin by his side, and every few minutes he gags and brings up a clear, frothy liquid. He has also vomited several times to-day. The temperature this evening is 103°; pulse 120, small in volume. The abdomen is soft, nowhere tender; the liver is not enlarged. Deep pressure just in front of the tenth rib causes him to wince. The urine was very much bile-stained. The patient was ordered oxalate of cerium and small quantities of liquid nourishment.

On the 10th and 11th the vomiting persisted, and the jaundice became much more intense. On the 12th and 13th he was a great deal better. He retained his food, and the distressing gagging had stopped. The temperature range was from 102° to 103.5°. The pulse was rapid, and he was still excessively nervous.

On the 16th and 17th the temperature was lower and he had profuse sweats. The abdominal symptoms were slight; the stools, which during the jaundice were quite clay-colored, by the 20th were again bile-stained, and at this date the jaundice had almost disappeared. The temperature on the evening of the 22d was only 100°; general condition excellent.

Severe toxic jaundice is exceedingly rare in typhoid fever. The

most carefully studied case I know of is that reported by Sabourin.[1] A man, aged twenty-nine years, who had always enjoyed good health, was admitted to Prof. Jaccoud's service in about the third week of typhoid fever. He had very intense icterus, great prostration and delirium, and with these symptoms frequent epixtaxis and hemorrhages from the intestines. The liver at autopsy was reduced in size, soft, and in a condition corresponding microscopically to acute yellow atrophy.

In the following case the jaundice developed at the end of the second week with much delirium, and the patient died in a condition of toxæmia with low temperature.

CASE II. *Severe attack; jaundice at the end of the second week; much delirium; low temperature; nystagmus; death on the sixteenth day.*—April 8, 1894. I saw to-day, with Dr. Martenet, A. B., aged thirty-five years, a healthy man, who had been attacked two weeks before with typhoid fever, all the symptoms of which had been very well marked. This was the fifteenth day of the fever. The temperature has been high, ranging between 104° and 105°. The rash was well developed and the spleen enlarged. The general symptoms were of only moderate severity. He had very slight diarrhœa.

For four days the patient has had a falling temperature, and yesterday morning, April 7th, it reached 98°; last evening it was 98°; this morning it was 97.2°. With this the general symptoms have been very much worse. He has been delirious; the abdomen has been distended, and jaundice developed on the evening of the 6th. This morning the patient is delirious, unconscious, and the jaundice is of considerable intensity. The eyes are open, and they are jerked in a quick way from side to side, looking like exaggerated nystagmus. The tongue is dry, the abdomen distended, not tender. The liver-dulness is not obliterated. The heart-sounds are clear. The pulse is 120, full, not dicrotic, and I noted particularly that it was of fairly good volume. On returning home, in the note I made of the case I added that though he looked so ill, and though the meteorism, jaundice, and low temperature, with the delirium, were unfavorable, yet the pulse-volume was remarkably good.

Death took place at three in the afternoon. There was no autopsy.

Jaundice would appear to be more common in the tropics. Alexander Jamieson,[2] in an admirable discussion of typhoid fever as met with in China, cites nine cases in which deep jaundice occurred. Of these four died. He thinks it is more fatal the earlier it develops.

[1] Revue de Médecine, 1882.

[2] Imperial Maritime Customs Medical Reports, 37th issue, 1891.

III. Abscess.

1. *Suppurative Pylephlebitis.* This is an excessively rare sequence of the disease. I have seen one instance of it which is given in full in my "Pathological Report No. 1," from the Montreal General Hospital. I will give here a brief extract:

A man, aged thirty-seven years, had an attack of typhoid fever three months before, from which he had not recovered. He had empyema and septic symptoms. So far as I could learn, there were no symptoms pointing to any trouble in the liver. He succumbed to an attack of acute peritonitis. The peritoneum contained eighty ounces of turbid fluid and was intensely inflamed, particularly about the appendix vermiformis, the cæcal end of which was obliterated, while the wall presented an oval perforation. There were fifty-four ounces of pus in the left pleura; both lungs presented numerous miliary tubercles. The mesentery was greatly enlarged and thickened, and fluctuated like a sac of pus. After incision and washing, it appeared riddled by communicating cavities, some of which could be traced in direct connection with mesenteric veins. The liver was enlarged, and presented, on section, numerous abscesses which were in direct connection with the suppurating portal vein. Outside the liver the vein was represented by an elongated abscess with thick, irregular walls. The splenic vein ended abruptly on the wall of the suppurating vessel, being closed by a thrombus. The branches of the portal vein in the liver were found to be full of pus, in some cream-colored, in others tinged with bile. The main branch passing to the right lobe, at about an inch and a half from the fissure, widened into two large sinuses. The gall-bladder contained three ounces of pus. At the upper part of the opening of the cystic duct there was an irregular, wide sinus leading toward the portal fissure, and along it a probe could be passed for nearly an inch and a half, terminating close to the dilated and suppurating branches of the portal vein.

Lannois[1] has reported an interesting case of pylephlebitis following typhoid fever, in which the Eberth's bacillus was found in the pus. He gives a reference to a number of other cases in the literature.

In a paper by Ernst Romberg,[2] of the Leipsig Clinic, of 88 fatal cases among 677 there was only one instance of abscess of the liver (suppurative pylephlebitis).

A man, aged thirty-four years, with well-developed typhoid fever, was admitted August 14th. There seemed nothing special in the case until Sep-

[1] Revue de Médecine, 1895.
[2] Berliner klinische Wochenschrift, March 3, 1890.

tember 7th, when he had a chill. On the 8th there was slight jaundice, which increased on the 10th and 12th. There was enlargement of the liver. The patient died on the 15th. There were healing ulcers in the ileum. There was a diffuse, suppurating phlegmon in the mesentery. The liver was enlarged and showed very extensive suppurating pylephlebitis.

This case resembles the one I have reported, inasmuch as it had the suppuration in the mesentery. Romberg refers to several others in the literature.

2. *Solitary Abscess.* This is very much more rare than pylephlebitis. In nearly one hundred autopsies in the disease I have not seen an instance. In their monograph on *l'Hépatite Suppurée*,[1] Bertrand and Fontan refer very briefly to this association, and state that it is relatively more frequent in the typhoid fever of the tropics.

In China, Jamieson,[2] in reporting a number of cases of enteric fever with dysentery, mentions a case of liver abscess. It did not seem to me altogether clear on reading his report whether the case was one of typhoid fever, or whether it was not an unusually severe and protracted instance of dysentery. The colon was much ulcerated, and an ulcer had perforated the cæcum. The note on the small bowel was "the lower end of the ileum was sown with circular ulcers in the midst of infiltrated areas, some of which had not broken down, corresponding to Peyer's patches."

The enormous Munich statistics of 2000 post-mortems in typhoid fever give twelve cases.[3] Other large statistics quoted are those of Dopfer, who in 927 cases of typhoid fever found abscess of the liver in 10 cases.[4] (Probably these cases are included in the other Munich statistics.)

3. *Suppurative Cholangitis.* Apart from the gall-bladder complications, which will be considered separately, abscess of the liver may be due to suppurative cholangitis. The cases are very rare. Klebs has reported one in his *Handbuch der Pathologische Anatomie,* in which the bile-passages within the liver were dilated into large cylindrical cavities containing necrotic yellowish material. The common duct showed no trace of any change.

4. *Secondary to the Complications of Typhoid Fever.* Romberg refers to an interesting group of cases in which the abscess is second-

[1] Paris, 1895.
[2] Loc. cit.
[3] Münchener med. Woch., 1891, Nos. 3 and 4.
[4] Ibid, 1888.

ary to some of the inflammatory sequelæ of the disease. He quotes a case from Louis in which liver-abscess followed abscess of the right parotid; a case from Chvostek, in which two large liver-abscesses were found in connection with perichondritis of the larynx in typhoid fever, and two cases in which the abscess followed peripheral bone lesions in the disease.

IV. Affections of the Bile-passages.

Much more common are the complications and sequelæ of the bile passages in typhoid fever. The subject may be discussed under three headings, namely, the incidence of typhoid bacilli in the gall-bladder in the bodies of persons dead of typhoid fever; the occurrence of acute cholecystitis and cholangitis during and after typhoid fever; and the relation of typhoid fever to gallstones.

(*a*) *The incidence of typhoid bacilli in the gall-bladder in typhoid fever.* Blachstein[1] in 1891, working in Welch's laboratory, found that after inoculation in rabbits the Eberth bacillus lived in the bile-passages for a considerable period of time, in one case for fifteen and a half weeks. He showed also the great frequency of the infection of the bile-passages with the colon bacillus.

It had been shown by Netter,[2] Letienne,[3] and others, that the bile-passages were quite frequently the seat of growth of micro-organisms; thus in 24 of 42 cases examined by the latter author, micro-organisms were present, of which the most common were the stapyhlococcus albus and the bacterium coli commune.

Experimentally, too, Gilbert[4] has produced cholecystitis and cholangitis by the direct injection of typhoid bacilli into the bile-passages, and in two dogs has produced also secondary endocarditis.

Dupre[5] found pure cultures of typhoid bacilli in two cases of typhoid fever; one dead during the fever, the other following an operation for gallstones six months after recovery from an attack of enteric fever.

A number of careful studies have been made upon the frequency of infection of the bile-passages in typhoid fever. Dr. Flexner has very kindly looked up for me the results of the examinations which

[1] Johns Hopkins Hospital Bulletin, 1891, vol. ii.
[2] Progrès Médicale, 1886.
[3] Arch. de Méd. Expérim., 1891.
[4] Soc. de Biologie, 1893-'94.
[5] Les Infections Billares, 1891.

have been made in the Pathological Laboratory of the Johns Hopkins Hospital. Cultures were made in fourteen cases from the gall-bladders of persons dead of the disease. Typhoid bacilli were present in seven instances. In five cases other organisms were found; in three the bacillus coli communis; in one the streptococcus pyogenes; in one the proteus. In one case the nature of the organism was not fully determined. In looking over the histories of the seven fatal cases, from the gall-bladders of which the typhoid bacilli were isolated, there were no hepatic symptoms, so that the infection was latent.

Other observers have found the typhoid bacilli much more frequently. Chiari's[1] studies have been, perhaps, the most important. He examined twenty-two cases, and found the typhoid bacilli in nineteen. In most instances the bacilli in the gall-bladder were in large numbers. He gives very full details of the observations, and what is very interesting, too, the stage at which the examination was made. Thus, of two cases in the stage of infiltration, in only one did the gall-bladder contain Eberth's bacillus; of seven cases in the stage of necrosis, five gave positive results; of six cases in the stage of ulceration, the gall-bladder in all contained the bacilli; of four cases in the stage of healing, all were positive; of three cases of relapse, in two the results were positive. In ten of the cases the gall-bladder showed more or less signs of inflammation, and in three there were areas of necrosis in the mucosa. In one case only was the whole thickness of the wall involved and the peritoneal covering. Chiari suggests that possibly in some cases the relapse may be due directly to the bacillus in the bile-passages. Thus he thinks that a very abundant meal, by causing an unusual flow of bile into the bowel, might in a case with numerous bacilli in the gall-bladder cause a reinfection of the lymph elements in the intestine.

Gilbert and Girode[2] state that in a case dead of typhoid fever they found the gall-bladder full of mucus and pus, and the mucous membrane inflamed. Cultures showed the presence of the typhoid bacillus.

Chantemesse[3] mentions the case of a woman who had had typhoid fever eight months previously, without any jaundice, but with a somewhat tardy convalescence. She was seized with hepatic colic,

[1] Prag. med. Woch., 1893, and Zeitschrift f. Hygiene, vol. xv.
[2] La Semaine Médicale, 1890, x. p. 481.
[3] Traité de Médecine, t. i. p. 764.

icterus, and fever. The gall-bladder, which was removed during life, showed the presence of gallstones with living typhoid bacilli.

(*b*) *Cholecystitis and cholangitis as complications and sequelæ of typhoid fever.* From what has been said in the previous section, it is very evident that the bacilli may be in the gall-bladder in numbers, and for a long period of time, without exciting any inflammation. Chiari's observations would warrant the conclusion that cholecystitis without any actual symptoms was by no means an uncommon event in the disease. In reality systematic writers have for a long time recognized the importance, both clinically and anatomically, of the gall-bladder complications of the disease. It is sufficient for the purpose to quote from Murchison's well-known work:[1] "The lining membrane of the gall-bladder is very liable to become inflamed in enteric fever, without producing any marked symptoms during life." He gives numerous references, and describes catarrhal, purulent, diphtheritic, and ulcerative forms with perforation. Under the complications and sequelæ he mentions a case in his own practice of perforating ulcer of the gall-bladder, and refers to other instances in the literature.

Of late years the subject has attracted rather more attention, and I may mention a few of the more important papers. Holscher,[2] in an analysis of 2000 cases of fatal typhoid fever, states that in five there were diphtheritic processes in the gall-bladder with separation of the mucous membrane, and suppuration. In one case there were perforation and peritonitis. I have already referred to the case of Chantemesse, in which eight months after the typhoid fever the patient had acute cholecystitis, and typhoid bacilli were found in the gall-bladder, which was removed during life. The question has assumed very practical aspects now that surgeons are called in early in these acute abdominal complications. Williams and Shields[3] report an exceedingly interesting case, in which a woman, aged thirty-one years, in the sixth week of typhoid fever, was seized with symptoms of perforative peritonitis. Laparotomy was performed, and the gall-bladder was found adherent, the walls thickened, and near the neck was a perforation in an ulcer, through which fluid was

[1] Continued Fevers, third edition, p. 634.
[2] Münchener med. Woch., 1891.
[3] Lancet, 1895, vol. i.

escaping into the peritoneum. There was suppurative cholecystitis without stones. The patient recovered.

A case of much interest is reported by H. B. Anderson,[1] of Toronto:

A man, aged sixty-seven years, was admitted to the Toronto General Hospital September 16, 1895. He had been ill in Detroit in July, with fever, chills, vomiting, and diarrhœa. He left Detroit before he had fully recovered, and was admitted to the hospital in Toronto on the above-mentioned date. Malaria had been suspected, but Dr. Anderson failed to find the plasmodia. There was a marked leucocytosis. There was intense pain on the right side of the abdomen and over the hepatic region, which, with a localized swelling beneath the ribs opposite the ninth costal cartilage, made the diagnosis of abscess of the liver very probable. The local symptoms subsided, but later there was general abdominal pain, with great aggravation of the symptoms, and he died September 26th, the eleventh day after entering the hospital.

The autopsy showed a general peritonitis; ulceration of Peyer's patches at the lower end of the ileum; acute cholecystitis, with ulceration of the mucosa, and in one place perforation of the gall-bladder. A bacillus was found in the gall-bladder, but whether the typhoid or the bacillus coli communis was not satisfactorily determined.

A very instructive case is reported by Dr. Alexieef, of Moscow. (I am indebted to the author for a copy of his paper, and to my associate, Dr. Thayer, for the translation from the Russian):

The patient, a child aged five years, had, during November, 1895, enlarged glands on the left side of the neck, which suppurated, and on the 18th were incised. Subsequently she developed very well-marked symptoms of typhoid fever—rose-spots, enlarged spleen, delirium, tenderness in the ileo-cæcal region, and high fever. During the third week in December there was marked pain in the right side of the abdomen, and a pear-shaped tumor was felt below the costal margin. There was fremitus felt between the 18th and 20th. Between the 20th and 22d the patient complained a great deal of abdominal pain, and became much excited. The abdomen was much distended and very tender; there was no jaundice. The tumor formerly made out could not be detected.

A diagnosis of cholecystitis was made and an operation was performed. The intestines were found adherent to the gall-bladder, which contained pus and had apparently perforated, as there was pus outside of it in the adherent tissues. It was packed and drained. The cultures were very carefully and thoroughly made, and the author concludes that the organism found was the bacillus typhi abdominalis.

[1] Canada Lancet, 1896.

The child improved very rapidly, and the first week in February the temperature was normal. After the 15th, however, she had fever and a slight relapse.

The author believes that between December 21st and 22d, when the patient had such extreme abdominal pain and collapse, that the gall-bladder had ruptured. He regards the lymphadenitis as a separate affair altogether.

It is worth noting that the child's mother was ill at the time with typhoid fever, and died during a relapse.

At a meeting of the Royal Medical and Chirurgical Society, January 26, 1897, Dr. Francis Hawkins read a paper on "Jaundice and Perforation of the Gall-bladder in Typhoid Fever" (*Lancet*, January 30, 1897):

He reports the case of a girl, aged eighteen years, who, during an attack of typhoid fever, had pain in the abdomen, particularly in the right epigastric and hypochondriac regions, with vomiting and increase of the fever. On the following day the conjunctivæ and skin of the upper part of the body were jaundiced, and bile was found in the urine. The jaundice became more marked and the pain more severe, and there was exquisite tenderness in the region of the gall-bladder. The jaundice persisted till death, lasting for three weeks. There were pulmonary complications, of which she died. The gall-bladder was adherent to the peritoneum, and around the adhesion there was a small area of peritonitis. The anterior wall of the bladder showed a perforation. The contents of the gall-bladder were purulent, and there was a gallstone lying free in it. There was typical typhoid ulceration in the intestine.

The following cases have come under my observation within the past two years:

CASE I. *Typhoid fever: pyrexia of exactly twenty-seven days' duration; attack of colic, probably from gallstones, during convalescence; good health for nearly seven months; acute suppurative cholecystitis; perforation of gall-bladder; operation; recovery.*—Miss J., aged twenty-nine years, a nurse, was admitted to ward C, April 22, 1895, on the fourth or fifth day of typhoid fever. She had a very characteristic attack, with numerous rose-spots. She had no serious symptoms, though the fever was high, ranging during the first ten days between 103° and 105°. She took exactly one hundred baths, and on May 18th the temperature for the first time touched normal.

On May 22d she had an attack of sudden, severe pain in the right hypochondriac region; the temperature rose to 102°, without a chill, and she had fever for thirty-six hours. There was no jaundice. Some time after she left the hospital, on June 21st, she had a second severe attack of pain in the same region, of great intensity. It also was not followed by jaundice. Each of these attacks was of great severity and required morphine. She had never previously suffered from similar attacks. She went home for the

summer and had two other attacks, each lasting about eighteen hours. There was no jaundice, and she felt well and gained in weight and strength. She returned to her duties at the hospital in October, and seemed to be doing very well. On the morning of December 23d she went on duty, feeling in excellent health. At 11 A.M. she had a feeling of distress in the epigastrium, and at noon, when she went off duty, she vomited. She returned to work at 3 P.M., and at 5 P.M. she vomited again, and an attack of pain came on in the right iliac fossa, very sharp and severe. When seen by Dr. Thayer at 11.45 P.M. she was in a great deal of pain; temperature was 101°. The pain came on in paroyxsms, lasting for a minute or more. The abdomen was flat, but over the entire right side there were muscular rigidity and a great deal of tenderness. The pain was localized in a small area close to McBurney's point. Any palpation in that region was very painful. Pressure on the left side of the abdomen caused a dragging sensation and pain between the navel and the anterior superior spine of the ileum. The bowels had been moved by injection during the day. She had a hypodermic injection of morphia, and she had a very good night, except for recurring attacks of cramp-like pains. The highest temperature reached was 102.4°.

At 9.15 A.M. on December 24th the attacks of pain were still recurring, with intervals of comparative ease. I saw her early this morning, and it was impossible to make a satisfactory examination. There was no abdominal distention, but a great deal of tenderness over the whole of the right side, which had increased a great deal. She was seen by Dr. Halsted, who concurred in the diagnosis of appendicitis. She became very much worse through the day. She had vomiting and the tenderness was very much more marked, and the general condition was evidently becoming more serious.

Dr. Halsted operated at six in the evening. An incision was made for appendicitis. There were a few old bands of adhesion seen about the cæcum, but the appendix was not found, and it was evident that the seat of the trouble was not here. Just above the cæcum the omentum was seen, adherent to the ascending and hepatic flexure of the colon. In it was a small opening from which a thin, yellow material flowed. At first this was thought to be perforation of the intestine in an old typhoid ulcer, but on enlarging the opening was found in the gall-bladder to which the omentum was adherent, and in the adhesions between the liver and colon there were several small pockets containing purulent, yellowish material. The gall-bladder was enlarged and very tense; 100 c.c. of a clear fluid were removed, after which flowed out about 30 c.c. of thick, purulent matter. The cystic and common ducts were explored, and it was thought that a stone was felt in the cystic duct, but on account of the depth of the duct and the numerous adhesions, and the difficulty of preventing infection of the peritoneal cavity, the gall-bladder was packed with gauze and the opening about it closed.

The patient did very well. On February 1st, upon introducing a probe into the sinus, a stone was felt, which gradually came out. She was discharged February 19th, and has remained well ever since.

CASE II. *Severe typhoid fever; protracted convalescence; pain in region of gall-bladder; jaundice; chills; phlegmonous cholecystitis; laparotomy; death.*—On November 5, 1894, I saw, with Dr. Booker, Mrs. A., aged thirty-seven years, married, who was in about the end of the third week of a very severe attack of typhoid fever. She was a very stout woman, and the symptoms had been severe: high fever, much prostration, and pronounced nervous symptoms. The attack was very protracted, and she was in bed for between nine and ten weeks. I did not see her again until called in consultation in the private ward of the Johns Hopkins Hospital by Dr. Bloodgood, a day or two after her admission on January 28, 1895.

On January 7th she had been attacked suddenly with severe pain in the epigastrium, passing round the right side to the back. She had no chill. The pain continued with severe exacerbations, and on the fifth day after the onset she became jaundiced. There was no positive history of fever, and she does not know whether she felt very hot. The bowels were loose and she had no vomiting. She was in bed, with more or less pain at intervals and with jaundice, without much change in her condition until January 21st, when she had a severe chill.

On the 27th the temperature rose to nearly 105°, and she had nausea and vomiting. On the morning of the 28th the temperature was 103.2°.

On admission the patient looked very ill, and she had vomiting, much thirst, dry tongue, pulse 124, and the temperature at eight in the evening was 103.8°. She was very stout and deeply jaundiced. The abdomen was distended and so tender that it was impossible to make a satisfactory examination. The condition was very serious, and Dr. Halsted performed laparotomy on the 29th.

The surgical note states that on opening the abdomen the liver was seen to be enlarged, the gall-bladder projected below the right margin, and on its anterior wall a rupture was seen through which bile and purulent matter were oozing. The wall of the gall-bladder in the neighborhood was quite necrotic. The gall-bladder was incised and drained and packed.

Cultures were made from the contents of the gall-bladder, and the colon bacillus was found. The colonies were worked over with the greatest care with reference to the differentiation of the typhoid from the colon bacillus.

The temperature fell after the operation and became normal on February 1st. She did very well for ten or twelve days; then she began to have nausea and vomiting, with marked reduction in the amount of the urine. There was no change in the jaundice, and she sank and died on February 21st.

CASE III.—*Fever of eighty-two days' duration; very slight remissions; a few rose-spots; general picture that of typhoid fever; occasional diazo reaction of the urine; Widal's reaction doubtful; no leucocytosis; spleen palpable; on the thirtieth day of the fever an attack of pain in the right hypochondriac region with great tenderness beneath the costal border; no chill; followed two days subsequently by slight jaundice; persistence of the fever; slight enlargement of the liver, with increasing tenderness in the hypochondriac region; exploration of gall-bladder;*

walls thickened; no stone felt.—Mrs. D., aged fifty-four years, admitted to ward G, November 9, 1896, on the eleventh day of an illness, with fever, loss of appetite, and weakness.

The family history was good.

Personal History. She has been a very healthy woman; has had eight children. Her only serious illness was in her thirty-fourth year, when she was in bed for four weeks with "inflammation of the stomach."

This spring, in the country, she had an attack of intermittent fever, chill every other day for a week, no jaundice. She was readily cured. When the patient came back from the country in July she had again six or seven chills. She appears to have had these for nearly ten years in the summer, when she went to the country.

On Wednesday, October 27th, the present illness began, with soreness of the throat, headache, and loss of appetite. She had been feeling a little out of sorts previously, and had had slight headache. She had pain in the back and limbs, and the following day she vomited and had pain in the epigastrium.

On October 30th she felt so ill that she went to bed, and was unable to eat on account of the fever. She had to get up and about for part of each day, until November 7th. The bowels had been constipated; she had had no chill, and, so far as one could gather, no local symptoms of any sort.

She was a large, stout woman, with dull, heavy facies and a muddy complexion. The tongue had a pasty, white coat. The pulse was feeble and small. The heart-sounds, too, were distant and feeble, apparently without murmur.

The abdomen was relaxed, everywhere soft, slight tenderness on pressure in the epigastrium. The border of the liver could be felt just below the costal margin. The hepatic flatness was at the seventh rib, in the mid-clavicular line. The spleen was easily palpable, and seemed hard.

The blood was examined on the 10th and 11th for malarial parasites, but none were found. Leucocytes were 12,000 per cm.

The patient presented a very dull, apathetic appearance, suggestive of typhoid fever; the spleen remained palpable. There were no very definite rose-spots noted. There were numerous pigmented spots over the abdomen, which looked like faded roseola.

Patient's temperature for the first ten days ranged, as a rule, from 101° to 104°. She had sponges, and on the 15th she began the tubs, which did not depress the fever very much.

For the second ten days, between November 19th and the 29th, the temperature range was a little lower. She still had a continued fever, often with very slight diurnal variations; thus, on the 26th, 27th, and 28th, the maximal diurnal range was, even with the tubs, only from two to two and a half degrees. On November 28th the patient complained of pain in the right side of the abdomen, and said that it hurt her to lie on this side. There was no difference on inspection, but there was greatly increased resistance in the right hypochondriac region below the costal margin, with tenderness.

She flinched at once on pressure over the region of the gall-bladder. She was nauseated and vomited, and any pressure in the right hypochondrium caused nausea. The leucocytes were 8000; she had no chill.

On the 29th and 30th the tenderness persisted beneath the right costal border, and on account of it it was very difficult to make a satisfactory examination. On the morning of the 30th the patient was jaundiced, the skin of a slight saffron color, and the conjunctivæ distinctly tinged. The urine was very high colored and showed reaction for bile-pigment.

On the 2d and 3d there were a couple of rose-spots in the right flank. On December 3d it seemed that the liver was enlarged; a resistant mass could be felt below the costal margin, difficult to make out on account of the tenderness. The jaundice gradually disappeared and the pain lessened, and by December 6th the color looked natural.

For the third period of ten days, from the 29th to the 9th, the temperature kept up, the maximum reaching between 103° and 104°. She continued to have the baths, on the 8th having her forty-ninth.

From December 9th to the 19th her condition remained much the same. She had no diarrhœa; the spleen continued palpable; there was no leucocytosis. The pain in the right side had disappeared a great deal. There seemed still a fulness under the costal border, but nothing very definite could be made out. On the 19th she complained again of pain under the right border. There were no rose-spots. The fever-range was not so high, between 100° and 102°; no sweats; no chills.

From December 20th to the 30th the patient presented very little change. The temperature-range was very uniform, between 100° and 102°. She remained very dull and heavy and apathetic. She still had pain on deep pressure below the right costal margin; the spleen was palpable. On the 31st the patient had an attack of vomiting.

The fever between December 31st and January 10th was a little higher, reaching sometimes 103°.

On the 5th Dr. Thayer noted that the abdomen was more flaccid; recti were still held tense on the right side of the abdomen. The border of the liver could be felt in the nipple line 13½ cm. from the costal border. Toward the rectus the edge of the liver is lost in the median line; the border is distinctly felt.

On January 6th I noted that the gall-bladder could not be felt distinctly.

On January 10th the temperature reached nearly 102.8°. The patient had nausea and a good deal of pain in the upper abdomen. She again had vomiting and pain on the 12th, and the temperature this morning was 103°.

On January 15th, 16th, and 17th the temperature was singularly uniform, not ranging more than half a degree from 102°.

About this time Dr. Halsted saw her, and thought with us that the symptoms pointed to some gall-bladder complication. The fever had persisted so long; the local tenderness had of late been increasing, and there seemed to be a tongue-like enlargement of the right lobe of the liver, so that on the 17th the patient was transferred to the surgical side for an exploratory opera-

tion. For the first time since her admission to the hospital, this morning the temperature fell to normal. The liver at the operation was enlarged, looked red and felt very firm. The gall-bladder was moderately enlarged, the walls seemed thickened; no stones were felt. It was not opened, as her condition became so dangerous that it was thought safer to close the wound.

June 1st she rallied from the operation, but has grown steadily weaker and thinner. The liver is enlarged, the skin is sallow, there is slight fever at times, but neither chills nor sweats. The nature of the trouble remains doubtful.

CASE IV. *Well-characterized typhoid fever in November and December*, 1895. *Readmitted November* 30, 1896, *in a febrile attack of about eight days' duration, of indefinite character; readmitted March* 5, 1897, *with high fever and great pain in the right side; development of jaundice; double parotitis; recovery.*—John Lehrman, aged twenty-four years, admitted March 5, 1897, complaining of fever and pain in the right side. He had been in the hospital from November 25, 1895, to January 1, 1896, with a continued fever, enlargement of the spleen, furred tongue, and several suggestive rose-spots. During this time the patient took twenty baths; the temperature fell to normal on December 5th, and he made a perfectly satisfactory convalescence. He had no jaundice and no signs of any trouble in the liver.

He was readmitted November 30, 1896, complaining of headache and weakness. His illness began about ten days before, with slight abdominal pain and loss of appetite. During the evening of the 28th he had a shaking chill, which lasted twenty minutes. This morning, the 30th, he had a second severe chill, lasting half an hour.

The patient was a well-nourished, healthy-looking man, with high color. The abdomen looked natural, no distention; the edge of the spleen could be just felt below the border; there was slight rigidity of the right rectus muscle and tenderness in the right iliac fossa on deep pressure. There were a couple of suspicious spots on his abdomen. During the next few days a blotchy erythema appeared very like urticaria, and very well marked dermatographia. There was no leucocytosis. His temperature was not high, having reached 103° on the day of admission, and then fell gradually and reached normal on December 6th. He had no further chills. He convalesced very rapidly. Widal's agglutination test was marked, but he had had typhoid fever in November, 1895. He was discharged on the 15th. The diagnosis was doubtful. There was nothing suggestive of liver trouble; he had no jaundice, but there was slight tenderness on the right side on deep pressure.

He was readmitted March 5, 1897, complaining of chills and fever. He had remained perfectly well until March 3d. At noon, on leaving work, he had a shaking chill, followed by high fever and sweating. He worked the next day (March 4th) until 10 A.M., when he had to give up work on account of severe headache and pain in the back. He had no further chill. He thinks he has had fever since the onset of the chills. The bowels have been constipated; he has had no vomiting and no sore-throat.

On admission the patient looked very well, though the face was flushed

and the eyes somewhat bloodshot. His general nutrition was excellent. He was a very powerfully built man; the lips and mucous membrane were very red; the tongue was brown in the centre and white at the sides; the breath was heavy. The temperature was 103° and rose at midnight to 105.5°. The pulse was 120, very full, and dicrotic. There were no rose-spots; no changes to be found in the thorax or abdomen. The edge of the spleen could be felt. The leucocytes were 4400 per cubic millimetre.

On the 6th Dr. Thayer noted that the hepatic flatness was at the sixth rib, and extended to one finger's-breadth below the costal margin. There was well-marked tenderness in the right hypochondrium on deep pressure. He winced at once on the slightest touch beneath the costal margin. The most tender point appeared to be just at the region of the gall-bladder. The temperature on the 6th was steadily between 103° and 104°. This morning the patient vomited a greenish, bile-stained fluid. He has a very flushed, congested appearance. The complexion, too, was a little muddy; the conjunctivæ looked a little suspicious, as though a little jaundiced. A very careful examination was made of the blood, but no malarial parasites were found.

On the 7th the temperature was lower, ranging between 102° and 103°. The tenderness was still very marked.

On the 8th the temperature was lower, in the neighborhood of 100°. The eyes were less injected and the conjunctivæ were a little yellow. He vomited this morning a greenish-yellow material. There is still a great deal of tenderness over the liver. To-day, for the first time, there is bile reaction in the urine; there has been a small quantity of albumin from the outset.

March 9th. Patient's temperature normal. Tenderness still very marked; no swelling; no increase in the area of liver dulness. Widal's test yields no reaction. Cultures made from the blood were negative.

10*th.* The patient is to-day distinctly jaundiced; the conjunctivæ are quite yellow and the skin of the trunk has a subicteroid hue. He has not nearly so much pain on deep pressure in the region of the gall-bladder.

11*th.* Temperature normal. To-day there are several slight hemorrhages in the conjunctivæ. The jaundice is quite marked. He complains to-day of a little soreness in both parotid regions, and cannot open his mouth well.

12*th.* Temperature rose to-day to 101°. Both parotids are a little swollen and sore. He is still jaundiced; no change in the general condition.

On the 13*th* and 14*th* the temperature was between 101° and 102° F.; both parotid regions greatly swollen. The tissues of the face and neck are infiltrated; the eyelids are œdematous; the skin over the most prominent portions of the glands is red, and there is a brawny hardness on palpation. The orifices of Steno's ducts are swollen, and a muco-pus can be squeezed out from them.

On the morning of the 15th the temperature was 103°. The patient's friends removed him.

Dr. Block kindly saw this patient after removal to his home, and reports that there were abscesses in both parotid glands, with much swelling and redness

of skin; incisions were made on the 20th. The patient stated that he felt much better. No jaundice, very little tenderness; temperature 100°; slight purulent discharge from ears, no rupture into mouth or pharynx. No tenderness over liver, gall-bladder, or any of the abdominal regions.

25th. No change in condition since last note, except that there is less purulent discharge. Patient feels well.

The patient returned to the ward for examination on March 31st. He had no fever; both parotid regions were still swollen and indurated, and showed behind the ears the healing scars of the incisions. There was purulent discharge from both ears. He had lost a great deal in weight. The abdomen was soft, very easily palpated, and there was no tenderness in the region of the liver. The gall-bladder could not be felt.

The first attack in November, 1896, and the second in March, 1897, were both doubtless due to cholecystitis—certainly the latter. Parotitis is a not infrequent sequel of acute inflammatory conditions in the abdomen, as pointed out by Stephen Paget.

(*c*) *Typhoid fever and gallstones.* Bernheim, of Nancy, seems to have been the first to suggest the possibility of a causal relationship between typhoid fever and gallstones. He states that he has three or four times seen attacks of colic in the course of typhoid fever in patients who had not before presented any similar troubles, and he asks whether it is not possible that the typhoid fever causes an alteration or a stagnation in the bile which predisposes to lithiasis in susceptible persons, or the typhoidal gastro-intestinal catarrh may be propagated along the biliary passages. Dufourt[1] has noted the existence of a previous typhoid fever in nineteen subjects of gallstones. None of these had had any signs previous to the attack. In twelve the first colic occurred in less than six months after the fever. Twice the attack occurred within two months, six times in three months, three times in the fourth month, and once in the fifth.

I have given the cases which came under our observation. In Case I. the patient had an attack of hepatic colic during convalescence and shortly after, and then remained perfectly well for nearly eleven months, when she had acute cholecystitis; perforation of the gall-bladder and gallstones were found. In Case II. the patient had an acute pain and symptoms of gallstones at the onset, but it proved to be an acute suppurative cholecystitis. In Cases III. and IV. it was not determined whether gallstones were present. It is

[1] Revue de Medecine, 1893, p. 13.

always worth while in the subjects of gallstone colic to inquire particularly with reference to the previous attacks of fever. In the following case the colic and jaundice developed within four weeks after convalescence:

CASE V.—G. W. R., aged twenty-six years (Hosp. No. 9331), was admitted March 4, 1894, with pains in the abdomen. Eight weeks before he had been laid up in Pittsburg for four weeks with typhoid fever. During convalescence he had a severe attack of abdominal pain similar to the present one, with much tenderness in the right hypochondrium. The jaundice, which came on two days after the attack, gradually disappeared, and the patient remained perfectly well until March 1st, when he again had an attack of severe abdominal pain, without chills or fever. This was followed by jaundice, which has continued, and for which he seeks relief.

He was a well-nourished, healthy-looking man, with jaundice of moderate grade. There was no enlargement of the liver. There was much tenderness beneath the right costal border and slight increase in the area of splenic dulness; the border was not palpable. The urine was high-colored and contained bile-pigment. The stools were white, and they were carefully strained for several days for gallstones without finding any.

Patient was discharged, much improved, on March 12th.

The infection of the bile-passages with the typhoid bacillus may, as we have seen, be perfectly harmless—that is to say, the gall-bladder may show no signs even of catarrh. In other instances intense cholecystitis may be excited, while in a third group the so-called lithogenous catarrh may develop from the irritation of the bacilli, leading to the formation of gallstones. Of course, it is quite possible that a patient with gallstones—and we know the percentage of those who have them is very large—may be attacked with typhoid fever, and the presence of the calculi in the gall-bladder may favor the settlement and growth of the bacilli, and it may not always be possible to determine which had taken place first.

I recently saw in the surgical wards with Dr. Cushing a remarkable case which illustrates a third possibility, namely, that the typhoid bacilli may, under certain circumstances, like the pneumococcus, be present without exciting the specific lesions of the disease.

CASE VI. *Gallstones; acute cholecystitis; typhoid bacilli cultivated from the gall-bladder; no previous history of typhoid fever.* (Through the kindness of my colleague, Professor Halsted, and of Dr. Cushing, who took the notes and made the cultures, I am enabled to refer to this remarkable case, which has a direct bearing on the subject in hand.)—Mrs. C., aged twenty-six years,

from Virginia, was admitted to the surgical ward, March 5, 1897, complaining of abdominal pain under the right ribs.

Personal History. She had had the usual diseases of childhood. With the exception of an attack of pneumonia, ten years ago, she has been a very vigorous, healthy woman. She has had no fever. She has been married five years; one stillborn child; one living child, two years old. She has been subject since childhood to indigestion and to prolonged attacks of constipation. About three years ago, and once each succeeding year, she has had attacks of vomiting, usually in the morning after eating heartily the night before. She is evidently a very careless eater, taking six cups of coffee a day, and is very fond of all sorts of salads and pickles. A year ago she had what the doctor called an attack of gravel. She had painful micturition, but no colic.

Present Illness. On March 1st, five days ago, after an enormous meal of beefsteak and gravy, the patient was seized at 4 P.M. with a mild pain in the right hypochondriac region. This continued until next morning, when she vomited both her breakfast and the dinner of the previous day. The quantity, she thinks, brought up was very large, at least two quarts. Soon after the pain became severe, and required morphine for its relief. Ever since the pain has been more or less constant under the right ribs; it is not paroxysmal, and does not radiate. She describes it as a soreness rather than as an actual pain. There has been no vomiting since the first attack; no jaundice. The physician who brought the patient to the hospital states that during these attacks she had fever, the highest temperature, 102°, on the third day of the attack.

The physical examination showed a dark-complexioned, large, well-nourished, well-developed woman, without jaundice. Pulse was regular, 90; temperature 101° F. The abdomen was full, tympanitic, and there was slight tenderness in the right hypochondrium, rigidity of the right rectus muscle, and on deep pressure an indistinct tumefaction below the costal margin. The edge of the liver could not be felt; the spleen was not palpable.

On March 6th, the day after admission, the indefinite mass, on deep palpation, was still present. The temperature was between 101° and 102°. During the next few days she improved; the temperature fell on the 7th to 99°. She had had her bowels freely moved, and on the 9th she was more comfortable than she had been since the attack. There was no rigidity, and the soft, movable mass could be felt deeply in the right hypochondriac region. It was slightly tender on the deepest pressure. The urine contained no albumin and no bile-pigment. The patient got up, and felt so well that she was anxious to go home. The right kidney could be readily palpated between the two hands. The mass at the right costal margin could be also felt readily, and was believed to be the gall-bladder.

Dr. Halsted operated March 16th, and found a large gall-bladder extending below the margin of the liver. When opened there was no bile, but a turbid, brownish, mucoid material, with fifteen large green faceted stones, varying in size from a pea to a cherry. One of the largest of the stones was removed

from the orifice of the cystic duct. The patient did very well until about March 20th, when there were signs of pneumonia of the right lower lobe. This, however, cleared up in a few days, and she made a rapid recovery by April 13th. She had a good deal of pain, and there was still a slight sinus with a little discharge.

The most interesting feature of this case relates to the bacteriological report, which will be published in full by Dr. Cushing. It is sufficient here to say that the cover-slips showed a few bacilli, and cultures showed a bacillus which presented morphological and cultural properties identical with that of Eberth's bacillus. What was also to be noted particularly was that the patient's blood gave the Widal reaction to the organism and also to another culture of typhoid bacillus.

The case which, so far as I know, is unique in literature, will be published in full by Dr. Cushing, with the necessary details about the cultures.

TYPES OF ŒDEMA IN INFANCY AND CHILDHOOD.

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ŒDEMA developing in early childhood, and especially in infancy, is sufficiently uncommon, as compared with its great frequency in adults, to render its occurrence a matter of interest, particularly as its etiology is often so very obscure at this time of life. Our attention has been turned in this direction through a series of cases recently under our observation, in some of which it was most difficult to determine the true nature of the affection.

In studying œdema as presented in early life one's thoughts naturally first turn to the possibility of the presence of nephritis. That this disease may occur in the very young has been amply shown by many writers, notably by Jacobi[1] and by Felsenthal and Bernard[2]. We have ourselves witnessed it repeatedly. Scarlatina is certainly one of its commonest causes, but it is well to remember that other infectious diseases, as measles, erysipelas, malaria, pertussis, diphtheria, and varicella, may be accountable for the renal inflammation, and that eczema and other cutaneous eruptions appear to be the cause in occasional instances. Intestinal disease is not infrequently the exciting factor in infants. Often we can discover no cause for the renal disorder, and sometimes we may be able to surmise only, as, for instance, when slight traces of redness or of desquamation indicate that possibly an erysipelas or a scarlatina has previously been present.

That congenital syphilis is capable of producing nephritis and consequent œdema is not yet universally admitted, although there

[1] New York Medical Journal, 1896, lxiii. p. 65. [2] Arch. f. Kinderheilk., 1893, xvii. 222.

are cases on record which appear to prove this with reasonable certainty. Yet these cases are rare. Audeoud,[1] in a recent careful paper, was able to collect but six instances, besides one reported by himself, of what seemed to be undoubted nephritis from congenital syphilis, as judged by the symptoms during life. The cases reported are those of Bradley,[2] Potain,[3] Coupland,[4] Coupland,[5] Massalongo,[6] and Hock[7]. In four cases autopsy confirmed the clinical diagnosis, and in three the evidences of nephritis and of syphilis disappeared under antisyphilitic treatment.

The two following cases observed by us are of interest in this connection:

CASE I.—Johnnie J., two months old; mulatto; seen for the first time January 21, 1897. The father acknowledged no symptoms suggestive of syphilis. The mother was apparently healthy and had had no miscarriages. Three other children were alive and well. When a month old the patient had some sort of erythema, which appears to have been slight and limited in extent. A week before his first visit he developed coryza badly. On examination the child was seen to be of a fairly healthy appearance. The nostrils were filled with a thick discharge, which interfered with respiration. On January 27th a desquamation was noticed over the hands, feet, face, and forearms. This was of a distinctly peeling character, suggesting scarlet fever; but interrogation of the mother failed to elicit the history of any eruption which would satisfactorily account for the symptom. A flat-papular, pale-red eruption, having all the appearances of syphilis, was present over the nates and especially about the anus and to a less extent over the thighs and about the knees. There was some excoriation about the anus. The nasal discharge was unabated. On January 29th the condition described was practically unchanged, and there was in addition evident œdema of the lower extremities and to a slight degree of the face also. Inunctions of mercurial ointment were ordered. This treatment was changed on February 1st to gray powder internally, owing to the dermatitis which had been produced. Improvement began and continued slowly. By February 13th the œdema was scarcely noticeable in the face, though still present to some extent elsewhere. The anal excoriations were healing and the rhinitis was much better. By February 16th the syphilitic eruption had nearly disappeared, and there was no more scaling, but still a little general œdema. Examination of the urine made about this time showed quite a thick ring of albumin with Heller's test.

[1] Rev. méd. de la Suisse rom., August 20, 1896, p. 381.
[2] British Medical Journal, 1871, i. 116.
[3] Gazette de Hôpitaux, 1878, 1201.
[4] British Medical Journal, January 31, 1880, 168.
[5] Transactions Pathological Society, London, 1875–'76, xxvii. 303.
[6] Ann. de derm. et de syph., 1894, 1148.
[7] Sem. méd., 1894, 475; ibid., 1895, 99.

Decomposition had advanced too far to permit of finding casts if present, but some leucocytes and small epithelial cells were observed. The child was seen for the last time on February 24th. It was then better in every way, although some rhinitis and œdema were still present.

In this instance it seems impossible to determine absolutely whether the cause of the nephritis was syphilis or scarlatina. The whole complex of symptoms, however, and the recovery under antisyphilitic treatment, leave us in little doubt that the nephritis was syphilitic.

The second case appears to be an undoubted instance of syphilitic nephritis, in spite of the failure to procure urine for examination.

CASE II.—Baby, R., male, born July 25, 1896. The mother appeared healthy; the father acknowledged having syphilis, and had symptoms of the disease. The child was small, thin, and weighed but four and three-quarters pounds. The skin of the feet and hands looked as though blistered, was cracked, and came off like a glove, leaving a raw, bleeding surface. Over the body, but especially on the limbs and around the mouth, nose, and anus, was an annular eruption, varying from pin-head to small-pea size. Coryza was present. Mercurial ointment was applied on the binder. On July 27th the eruption had become pustular, with thick crusts and fissures about the nose, mouth, and anus. Some small aphthous patches were present in the mouth. The child improved slightly, but on August 3d dropsy appeared in the legs, and by the next day involved the lower extremities, face, and abdominal cavity. Under the continued use of mercurial ointment, combined with diuretics, the œdema rapidly disappeared, as did the cutaneous symptoms later, and the child steadily improved in health, gaining two pounds by September 4th. It has continued well since this date.

In addition to the causes of nephritis mentioned there seems no reason why a general septic infection should not produce severe parenchymatous changes in the kidneys. The following case appears to be an instance of septic nephritis. The origin of the infection could not be discovered. All the tissues of the body were examined except the bones, and it is possible that a septic inflammation of these may have existed. The case occurred under the care of Dr. J. C. DaCosta, in St. Agnes's Hospital, Philadelphia, where we had the opportunity of seeing it. For the notes of the autopsy we are indebted to Dr. A. O. J. Kelly, pathologist to the hospital.

CASE III.—Eleanor M., born October 10, 1896, weight seven and three-quarters pounds. Except for slight ophthalmia and coryza, both of which

recovered promptly, the child was entirely well until December 31st, when feverishness and malaise developed. On January 1, 1897, the evident illness had increased; there was decided pallor, and the right leg from the knee down was swollen, as was also the vulva. The latter was red and angry-looking, yet without the appearance of erysipelas. By January 2d the œdema had extended to the thigh, and on this day or the next a swelling appeared over the left parietal bone. On January 3d swelling of the left elbow-joint set in. We saw the child on the morning of January 4th and found it very ill, seeming to suffer pain and crying weakly if disturbed. It was of a waxy pallor with a slight icteric hue, and the conjunctivæ were decidedly yellow. On the left parietal prominence was a large projecting swelling, very hard and the size of a walnut. The eyelids, both upper and lower, were œdematous, making the eyes appear deep-set and small. The rest of the face was slightly swollen. The left elbow presented a spindle-shaped swelling, somewhat tender, but not red. The right leg and thigh were very œdematous throughout, the swelling being tense but without redness. Both external labia were swollen and not discolored. Nothing abnormal could be discovered about the bones of the lower extremities. The ribs were slightly beaded. Examination of the liver and spleen gave negative results. A stool passed during the examination was formed and almost white. No temperature record was kept. The child died a few hours later. Urine taken from the bladder after death contained about one-sixteenth albumin by bulk, with leucocytes and numerous bacteria; but no casts could be found, the decomposition having doubtless destroyed any present. The autopsy showed that the parietal swelling had flattened very much after death. Pus was discharged on incision. The left elbow-joint was very much swollen, the bones being loosely attached and giving a rough sensation when rubbed together. The joint contained pus. The external genitals were much swollen. The right lower extremity was greatly swollen, pitted on pressure, and on incision discharged a clear serous fluid. The crural vessels were normal. The thoracic viscera showed nothing worthy of note except that the heart muscle was flabby, friable, and yellowish-red in color. Incision of the abdominal cavity revealed an acute general peritonitis, with recent adhesions and a sero-purulent fluid with flakes of lymph. The spleen was much enlarged, very soft, and dark reddish-brown; the liver enlarged and slightly fatty; the kidneys enlarged, soft, pale yellowish in color, with reddish areas, and with the cortex thickened. The other abdominal viscera and the internal genitals were normal. Microscopical examination of the organs showed slight fatty degeneration of the heart muscle and of the liver. There was general hyperplasia of the elements of the spleen. Many of the epithelial cells of the convoluted tubules of the kidneys had desquamated, and many had lost their outline, and their nuclei stained little if at all.

Children may develop an œdema, more or less general, in which no distinct evidence of nephritis exists. For instance, it sometimes happens that erysipelas neonatorum will leave a comparatively

extensive dropsy, yet without signs of renal disease. Sometimes scarlet fever is followed by dropsy, yet without albuminuria. Quincke[1] refers to an epidemic of scarlet fever occurring in Berlin, described by Phillip, in which anasarca developed in about one hundred cases, and in at least sixty of these no albumin could be discovered in the urine. Goodhart,[2] too, has reported similar cases, and warns against the hasty conclusion that nephritis is not present because there is no albuminuria. Dickinson[3] reports some interesting cases in which no cause whatever could be discovered for the widespread œdema, and in which there had certainly been no scarlatina, and no albumin could be found in the urine, yet in which autopsy showed the existence of nephritis.

As in adults, localized œdema may occur as the result of pressure upon venous trunks. This is, perhaps, oftenest due in children to the existence of enlarged bronchial glands. The existence of valvular cardiac disease may produce a general œdema in early life. So, too, any state of extreme exhaustion, debility, and anæmia may be attended by a marantic œdema in which no albumin may be found in the urine. In our experience this is proportionately much less common in infants than in adults, if we take into consideration the vast number of instances of marantic states which occur in early life. The causes of this œdema at any time of life are the same, viz., a hydræmic state of the blood and a tendency for the serum to leak through the vessel-walls. Some of the cases have been proved by post-mortem examination to be entirely free from renal disease, but in other instances the reverse was true.

In this connection we may refer to the strange disease known as œdema neonatorum. As Ballantyne[4] has well pointed out, this is rather a symptom of several conditions than a pathological entity. But until we understand the matter better it is convenient to classify these conditions together under the one name.

As ordinarily described, œdema neonatorum occurs usually in very weakly or premature infants. It generally but not necessarily begins before the third day of life. It is characterized by low temperature, coldness of the surface, and a widespread œdema, which

[1] Berlin. klin. Wochenschrift, 1882, xix. 57.
[2] Guy's Hospital Reports, 1884, xxvii. 197.
[3] Transactions Pathological Society, London, 1870, xxi. 255.
[4] British Medical Journal, 1890, i. 403.

pits on pressure, although with difficulty. The child is apathetic and unable to nurse, the pulse and respiration are slow and weak. Death nearly always takes place, but recovery is occasionally seen.

Whether or not œdema neonatorum is to be considered identical with sclerema neonatorum has been and still is a much disputed question. Parrot believed them different, and Ballantyne and others share this opinion; while, on the other hand, many describe them as identical or at least as forms of the same affection. There seems, we think, good reason to believe them entirely different, and it is even a question whether sclerema is at all to be classified as an œdema of any sort.

Œdema neonatorum and sclerema neonatorum are alike in their development in feeble and often in premature infants, in the low temperature present, and in the excessive weakness seen; but in sclerema the skin is hard and will not pit, cannot be pinched up into folds, is often discolored, seems adherent to the subjacent parts, and will not exude serum when cut at the autopsy. There is also rigidity of the whole body. It is certain, however, that the two diseases may be associated in the same case, as Parrot states.

Sclerema oftenest begins in the first two weeks of life, but may not develop until later. The induration is at first limited, but rapidly spreads over much of the body. A discoloration of the skin is often present, as already stated. Although often confounded with it, the disease is to be distinguished from scleroderma, which is a chronic, usually localized, and generally not especially dangerous affection of the skin.

Various theories have been advanced to explain the hardening of the skin in sclerema, among them being that it depends upon a thickening of the subcutaneous bands of connective tissue. Possibly, also, it is due in part to a solidification of the fat, depending upon its different constitution in very young children, as claimed by Langer.[1]

The following case of sclerema came recently under our observation:

Case IV.—John C., Italian, fifteen days old. The father and mother and two of their children were living and well. Two other children had died of causes unknown. The patient was said to have been ill for a week, with rapid

[1] Wiener Sitzunsbericht, 1881.

respiration and a cough, and had vomited milk at times. He was taken to one of the Philadelphia hospitals, where the diagnosis of pneumonia was made. No careful examination was given to the surface of the body, but slight subconjunctival hemorrhage was noticed. On the same day, or possibly the following day, the child was taken to the Children's Hospital, Philadelphia, where he was admitted February 6, 1897, at about 1 P.M. He was in an apparently dying condition, cold, stuporous, pulseless, with corneal reflex scarcely obtainable. The temperature in the rectum was 93.8° F., and the respiration 48. The mother called attention to the hardness of the cheeks, which she said she had noticed on that day for the first time. Ecchymotic spots were present on the eyelids, and these the father maintained had been there since birth. Discoloration of the nates resembling bruises were observed. This the father insisted had not been present before the child's visit to the hospital referred to. The child was at once put to bed and stimulants and external heat employed. After some reaction had occurred the chest was examined, and the physical signs of pneumonia found. At 6 P.M. temperature was 94° F. and respiration 42. During the night following the child had a convulsion. We saw it for the first time on the morning of the next day, February 10th, when it presented the following condition: it was evidently extremely ill, and lay for the most part perfectly still, with the eyes half closed. Respiration was rapid and shallow, the pulse feeble, the color pale and slightly cyanotic. Slight subconjunctival hemorrhage was present, and some small ecchymotic spots on the eyelids. Both cheeks appeared rather full, and on examination were found to be much thickened and of stony hardness, without the slightest pitting on pressure. There was no discoloration of them. Examination of the inside of the cheeks with the finger revealed nothing abnormal. Over the buttocks, lower part of the back and upper part of the thighs the tissues exhibited the same indurated condition, with a bluish, and in some places yellowish, discoloration, exactly resembling the colors of a bruise a few days old. This bruised appearance was best developed in the neighborhood of the anus. The thighs were hard, rigid, but not discolored except in the upper parts. During the morning of February 10th the temperature rose to 101° F. (possibly aided by the continued application of heat), the child had a few convulsive movements, and died at noon. No autopsy was allowed. Examination of the surface of the body after death showed that the blue color had faded to a slight extent. A faint bluish discoloration had appeared in a small spot near the navel. The induration of all the affected parts was unchanged, except being possibly a little less marked over the nates. The bladder was aspirated to obtain urine for examination, but without success.

Sclerema neonatorum is rare in all parts of the world. We have looked through the medical literature at our command in order to discover the cases reported in America, and have found but few. Some of these are of rather doubtful nature, while others are merely

referred to in the discussion which took place upon some of the papers contributed upon the subject. We have found but five fully detailed cases which exhibit the complex of symptoms usually considered characteristic of the disease. We have epitomized them as follows:

A. H. Robinson (*Arch. of Dermatol.*, 1882, viii. 337).—Well-nourished boy, seven months old, had many convulsions during the first day of life and intense jaundice on the third and fourth days. On the second day of life induration appeared over buttocks and extended half way down the outer aspects of thighs. Affected skin not unusually pale, and not cooler to touch; moderately œdematous. Temperature taken once registered 101° F. Child steadily improving at time of report.

In the discussion of this case:—

Weisse referred to two instances of the disease seen by him, in one of which the induration began at the back of the neck and extended over all the body and the back of the legs. Both cases recovered.

Piffard said he had seen one case.

Taylor had seen two cases, both in children two to three weeks old, and both terminating in recovery. The disease extended over the entire body.

In the absence of further details the suspicion is strongly aroused that these cases referred to in the discussion were instances of some form of œdema and not of sclerema.

Ellen A. Ingersoll (*Peoria Med. Monthly*, 1887–'88, viii. 240).—Mother alcoholic. Boy, well developed at birth. On third or fourth day of life scrotum and anterior surface of thighs became swollen and hard, the skin and subcutaneous tissue being involved. The affection spread over the lower extremities, then attacked face and neck, the chest and upper extremities. Death within forty-eight hours, apparently from involvement of muscles of respiration and deglutition.

W. P. Northrup (*Trans. Amer. Ped. Soc.*, 1889, i. 140).—Girl, five days old, one of twins, weighed seven pounds. Feet puffy, rectal temperature 96.5°, and remained low. Examination two days later showed induration throughout lower and upper extremities, hips, shoulders, scalp, and face; most marked on thighs, arms, and cheeks; least on abdomen; color brownish yellow. Body stiff and very cold, as though frozen. Rectal temperature would not reach lowest figures of the thermometer—*i. e.*, 96°. (See *Trans. Amer. Ped. Soc.*, 1893, v. 159.) Died on ninth day of life. Autopsy revealed no œdema; tissues cut hard; microscopic examination of skin showed nothing abnormal.

In the discussion of this case:—

Huber said he had seen a fatal case in a child several months old. The symptoms were identical with those described by Northrup.

Koplik said he had seen cases.

Holt reported a doubtful case in a child of thirteen days, in which scattered scleremato̊us patches appeared over the shoulders, back, arms, neck, and in the cheeks. The temperature was not subnormal. At the end of five months the patches had nearly disappeared. Later, Holt (*Diseases of Infancy and Childhood*, 1897, p. 117) says he has seen five cases.

L. F. Barker (*Trans. Amer. Ped. Soc.*, 1893, v. 142).—Boy, well developed at birth, taken with pneumonia when nearly nine weeks old. On eighth day of his illness skin on buttocks was found to be hard. By the next day whole body was of a woody hardness; skin could not be picked up, and was cold; limbs rigid; power of swallowing lost. The scrotum was the only portion not affected. The child died on the succeeding day. Temperature during the attack of sclerema was not depressed, and on one occasion reached 102.5° F. Autopsy showed skin of marble whiteness, without pitting on firmest pressure. It creaked when cut. Microscopical examination showed principally swelling and thickening of the fibrous bands of skin and subcutaneous tissue.

In the discussion of this paper:—

Jacobi stated that he had seen a few cases.

J. L. Porteous (*N. Y. Med Journ.*, 1893, lvii. 442).—Infant, sex not stated, developed the disease when two days old. When seen on the fourth day of life skin of legs, feet, arms, hands, back of shoulders, and upper part of chest "had the feeling of India-rubber stretched over a frame." Color varied from deep purple to pink. Cry feeble; respiration seemed difficult; child stretched itself frequently "as if it felt stiff all over." Temperature 97° F. Constipation obsinate; punctures of skin let out only a little blood and yellowish fluid. On sixth day of life temperature fell to 87° F., and child died.

There are besides these cases two which have sometimes been considered instances of sclerema, but which cannot be properly placed in this category. They are as follows:—

C. D. Smith (*N. Y. Journ. of Med.*, 1854, xii. 190).—Male child, (presumably) over a year old; well when born. At age of six weeks developed swelling of right hand, which progressively increased for six months, and then remained unaltered without extending. Child still living and in excellent health. Induration was as hard as marble, with the local temperature lower and the color whiter, but sometimes purplish. It was painless and would pit on pressure.

C. C. McDowell (*Maryland Med. Journ.*, 1877, i. 203).—Child of three weeks, had "the dermal lesion," involving the cutaneous surfaces largely

(but a nearer description is not given). Subject to attacks of partial pulmonary collapse, and with these the dermal lesion was "always exacerbated." It recovered after four or five weeks.

We have still to refer to that curious condition angioneurotic œdema, as it was first called by Quincke. This affection, not particularly common at any period of life, is certainly uncommon in early childhood and especially in infancy. The following case seems properly to belong to this category:

CASE V.—Andre P., aged two and a half months, of apparently healthy Italian parentage. The history could be obtained only with the greatest difficulty. It appeared that two other children were living and well. The patient apparently was well and properly developed when born, and remained in good condition until about one and a half months old, when red blotches began to appear in different parts of the body. These would last only a few hours in any one spot and be followed by œdema. The redness and œdema shifted from spot to spot, lasting a few hours to several days altogether. The bowel movements had been loose and green for about a week before the child was seen by us. The first examination, made June 18, 1896, showed the child to be much emaciated and decidedly anæmic. The heart and lungs appeared to be normal. The right hand and forearm were œdematous, pitting on pressure, and of normal color except for a glassy appearance. This condition was said to have been present for four days. The right leg and foot were swollen, and the mother stated that they had been more so, and that the genitals had been swollen also. The right side of the face was flushed and slightly harder than the left, but there was no distinct œdema of the face, although it was stated that there had been some that morning earlier. The temperature was 100° F. The urine contained no albumin. On June 19th the left little finger was œdematous and glassy in appearance. The redness of the face had disappeared. The right hand and leg were much swollen. The temperature was 99.2° F. On June 20th the œdema of the left little finger and of the right hand and forearm had disappeared, and that of the right leg was much better. There was swelling over the right biceps, which had developed during the night. It was the size of a walnut, red, painful, and very hard. The temperature was 100.2° F. A second examination of the urine was negative. By June 22d all œdema had disappeared except over the biceps, where it was somewhat larger and still slightly red. By June 25th this was less red, more glassy, and very painful. The disturbance of the bowels had continued more or less from the first visit.

The child was lost sight of until July 17th; then it was learned that the swelling on the upper arm had seemed obstinate in disappearing and that the child had been taken to some hospital. There it was supposed that an abscess was present and an incision had been made, but as far as could be learned no pus was discharged. The child was still thin, but appeared well in other respects.

Angioneurotic œdema is certainly closely allied to urticaria, and is, in fact, probably identical with the so-called giant urticaria. It is certainly related to some of the manifestations of peliosis rheumatica and Henoch's purpura. The following case, occurring in a child, illustrates a condition which might be described either as angioneurotic œdema or as purpura urticans. The element pointing toward the former is that the œdematous part of the body was but little affected by the urticarial eruption.

CASE VI.—Barty C., five and a half years old. On the evening of March 2, 1897, he developed a rash on the back and abdomen, which strongly suggested measles, yet without the characteristic grouping and with the presence of a few urticarial wheals. On March 3d the rash of the day before had become purpuric, and there was an additional development of a widespread erythema with wheals. The face was very œdematous, not flushed, and looking like a typical nephritis. By March 4th the eruption was rapidly fading and the œdema better, and by March 5th all symptoms had disappeared. Repeated examination of the urine had shown nothing abnormal.

The chief characteristic of angioneurotic œdema is expressed by the definition "acute, local transitory œdema." It is possible, however, as some cases have shown, for the œdema to be more persistent in character. As a rule, the swelling appears suddenly upon some part of the surface, perhaps always the same in each attack, or varying in locality in different attacks, or rapidly leaving one part to develop suddenly in another. It lasts hours or days. Gastrointestinal disturbances not infrequently accompany the swelling. Heredity has a very decided influence in many cases. Exposure to cold is often an active exciting cause. The disease is probably a vasomotor neurosis, as Quincke maintained. It is associated in some way with forms of urticaria and of purpura, as the case just detailed exemplifies.

Angioneurotic œdema developing early in life is rare, as we have said, yet it is noteworthy that one of the first reported cases (Dinkelacker) occurred in an infant. We have made some search, although not exhaustive, through medical literature for cases beginning in early life, but have found few. Very briefly abstracted they are as follows:

Dinkelacker (*Inaug. Dissertation*, Kiel, 1882).—Boy of one year had attacks of local œdema from the age of three months. The father was also subject to the disease.

Falcone (*Gaz. degli Ospitali*, 1886, vii. 125).—Boy of seven years had well-marked attacks. His grandfather also had the disease.

Widowitz (*Jahrb. f. Kinderheilk.*, 1886, xxv. 252; 1889, xxix. 388).—Three cases: 1st, a girl of seven years, in whom attacks of œdema of nose, cheeks, and fingers had occurred since age of four years; 2d, boy of eight years, in whom attacks of œdema of fingers and cheeks occurred from exposure to cold since age of six years; 3d, boy of six years, with swelling of face and often of fingers, resulting from cold.

Johnston (*Amer. Journ. Obstet.*, April, 1885, 393).—Five-year-old girl, affected since three months old. Feet and hands grew red, swollen, and painful. Attacks brought on by exposure to cold.

Josephs (*Berlin. klin. Wochenschr.*, 1890, No. 4, 77).—Five-year-old boy, affected since age of two and a half years. Swellings of unclothed parts when in cold wind. Had had an attack of hæmoglobinuria. An eight-year-old cousin had similar swellings.

Loimann (*Wien. med. Presse*, 1888, No. 29, 753).—Six year-old-boy, affected for three years. Attacked especially eyelids. Later, face and genitals.

Graham (*Ann. of Gynæc. and Pædiat.*, April, 1894).—Child of seven years nine months, affected since one year old. Frequent swellings of eyelids and face.

Mooney (*Detroit Med. Age*, 1895, xiv. 10).—Girl of nine years. Backs of hands attacked.

Yarian (*Med. News*, August 29, 1896, 238).—Woman had had attacks from childhood. Œdema, with vomiting, epigastric pain, and weak pulse. Mother had attacks from childhood. Maternal uncle affected. A girl cousin had attacks of œdema. Boy cousin had the disease and died at seven years. Maternal great-grandfather and grandfather and some of great uncles had periodical œdema.

Gevaert (*Rev. mens. des malad. de l'enfance*, 1894, xii. 369).—Girl of three years had transitory œdematous tumor of left side of neck.

Osler (*Amer. Journ. Med. Sci.*, 1888, xcv. 362).—Family history of five generations, twenty-two persons affected. Among them one man suffered from his youth; one girl of ten or twelve years was affected; one girl began when four or five years old; one girl had swollen ever since she was a small child.

Henoch (*Vorles. ü. Kinderkr.*, 8 Aufl. 612).—Four cases reported, the first evidently belonging here; the others not so certain and not called angio-neurotic. 1st. Girl of four years. Attacks of œdema of feet, hands, and face, with malaise and vomiting. 2d. Girl of four years. An attack of œdema of face and feet from exposure to cold. Pain in feet; anorexia and slight fever. 3d. Boy of nine years. An attack of œdema of face, scrotum, and prepuce. No cause found. 4th. Child of four years. An attack of œdema of face and thighs. No cause found.

Rotch (*Pediatrics*, 1896, 484).—Two cases. 1st. Boy of two and a half years. First attack at nineteen months. Eating of eggs would cause œdema of eyes. 2d. Boy of three years. Œdema of hands. Attacks ceased after circumcision of tight prepuce.

Masterman (*Brit. Med. Journ.*, 1897, i. 846).—Boy of eight years. Severe œdema of left leg and arm and of eyelids, with purpura and pain. Then of right arm with fresh purpura and severe pain. Later an attack of dysentery.

There are finally the cases of œdema occurring in infancy which are of entirely doubtful origin and nature. We have already referred to the element of doubt attending many cases. Milroy[1] reports an interesting family history, in which out of ninety-seven individuals in six generations twenty-two had been affected. The œdema involved one or both legs and was permanent. It was congenital in origin except in one case, beginning in this not until the age of twelve years. These cases were believed by Osler to be allied to angioneurotic œdema; but Milroy believed them rather to be dependent on some congenital absence of valves in the veins. They certainly do not present the complex of symptoms of angioneurotic œdema.

The following instance of œdema is allied in some respects to those of Milroy; and, like them, its nature seems entirely obscure. We had the opportunity of seeing the patient through the kindness of Dr. Arthur Van Harlingen.

Benny S., four years old, seen January 27, 1897. The mother was a healthy woman in appearance. There was nothing to note in the family history. Several other children were entirely well. The mother stated that the child was well when born, and remained so until he had measles at three months of age. The testicles and scrotum were said to have been very large at birth, but this enlargement disappeared later. At three months of age, or shortly afterward, swelling of the left leg and of the face began, and this has continued more or less ever since. At times the eyes had been so swollen that the child could hardly see. The swelling of the leg was constant, and, as it would appear, varied less than the swelling of the face. The operation of ritual circumcision had left œdema of the remains of the prepuce. The child had always been normally bright. The mother stated that the urine had been examined repeatedly and nothing ever found wrong with it.

Examination showed a child well-developed bodily for his age, but rather pale. The intelligence seemed to be entirely normal. The head was slightly asymmetrical, one parieto-occipital region being slightly flatter than the other.

[1] Omaha Clinic, 1892, v. 101.

The bridge of the nose was unusually broad and rather flat, this appearance being distinctly added to by a decided œdema of the tissues about the bridge. The eyes had a rather peculiar, deep-set appearance, this possibly being due to the œdema of this portion of the face. The left ankle and leg were swollen, giving the member a cylindrical form. The œdema would not pit on pressure, and was so firm that at first it seemed that the tibia itself was greatly thickened, but further examination made it reasonably certain that the bone was of natural size. The child had coryza at the time of the examination, and the voice was rather nasal. The examination of the urine a short time later was entirely negative in its results. Under treatment by pressure with medicated plasters the œdema of the leg diminished considerably. The case then disappeared from observation.

The peculiar persistence of œdema, and especially the localization to so great an extent in the left leg, made the case very obscure; and this obscurity was added to by the firmness of the swelling there. The expression of the face was decidedly suggestive in some respects of cretinism, yet there was no other symptom which supported this diagnosis. We are entirely unable to account for the condition.

The following instance of œdema of doubtful nature occurred in the Children's Hospital in the service of Dr. Alfred Stengel, where we repeatedly saw the case:

Harry B., twenty-three months old, admitted to the Children's Hospital November 7, 1896. Family history negative. Previous personal history good. The present illness began five weeks before with fever, diarrhœa, cough, and cold extremities. On entrance to the hospital it was found that the child's liver was enlarged, and there was dropsy of the feet, eyelids, and abdominal cavity. The urine contained no albumin. Examination on the following day showed the child to be evidently very ill, with cyanosis, great dyspnœa, œdema of lower extremities, and to a less extent of the hands, and the physical signs of fluid in the abdominal and right pleural cavities. The heart-sounds were practically normal. There was no evidence of pulmonary consolidation. The blood examination gave 65 per cent. hæmoglobin and 3,500,000 red blood-cells to the cubic millimetre. The liver extended almost to the umbilicus. This was apparently due partly to displacement by the pleural effusion, partly to actual enlargement. Under the administration of digitalis and purgatives the fluid disappeared from the abdominal cavity and the limbs, but that in the right pleural cavity continued to a considerable extent. On November 14th a second examination of the urine was made with negative results. On November 24th the fluid was still present in the right pleural cavity, but in less quantity. By November 30th it was decreasing here, but at about this date it was found to be accumulating in the left pleural cavity also. On December 11th fluid was still present on the left side and to some extent on the right. The temperature up to this date had

ranged from 99° to 100°, but it now rose to 103°, and varicella developed. This ran a moderately severe course, but disappeared without any sequelæ, the temperature now ranging about 99°. By December 20th the child was improving very much in every respect, although there was fluid still present in the left pleura. By December 31st no fluid was longer to be discovered. He was discharged cured on January 4, 1897.

The origin of the œdema in this case was at first entirely inexplicable. There existed no especial degree of malnutrition or anæmia which could account for it, or any albuminuria or evidence of an inflammatory process anywhere. Later when the fluid appeared in the left pleural cavity it appeared possible that the child might be the subject of general tuberculosis, and that the behavior of the effusion indicated tubercular pleurisy; but the subsequent course of the case renders even this improbable, and we are still in the dark regarding the nature of this case of anasarca.

No conclusions are needed as a closing to what has been said. It has been our object merely to impress the importance of careful and more extended study of the forms of œdema as seen in children, and to illustrate these forms by certain cases which have recently occurred in our experience.

A CASE OF LEVANT FEVER.

By A. ALEXANDER SMITH, M.D,
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So far as I have been able to ascertain, this is the first case of Levant fever reported in this country:

Mrs. G., thirty-four years of age; married eleven years; came under my observation on January 13, 1897. She lived in the United States until the autumn of 1885, when she went to Syria.

Family history. Father and mother are living and in good health. Brothers and sisters—five in all—in good health. No history of hereditary taint in either family of parents.

Previous history. The patient always enjoyed good health, with the exception of whooping-cough and measles in childhood, until the autumn of 1888, when she was compelled to leave Aleppo, where she had been for six months, on account of recurring attacks of intermittent fever. These attacks began with slight chilliness, the fever following being continued and lasting three or four days. The attacks came regularly once in two weeks. The last attack occurred in July, 1889, while travelling on the Cilician plain from Tarsus to Aintab. It was the most severe of all. During none of these attacks was the blood examined. She had lived, before her marriage, in a malarious region in Southern Iowa, but had never had any malarial manifestations before.

In the autumn of 1889 she removed to Beirut, Syria, where she was apparently perfectly healthy until the autumn of 1895. In the summer of that year she visited America, and became much run down while staying with her parents in Southern Iowa. Upon returning to Beirut she had an unusually severe attack of typhoid fever, the fever lasting more than six weeks, and with hemorrhages from the intestine in the fourth and fifth weeks. After recovering from the typhoid she regained her usual flesh and strength very rapidly, and was apparently in her usual health until July 4th following. On that evening she sat out rather late at a garden party. That night she began to have fever. It was of a remittent type, and lasted four weeks. There was no diarrhœa, no hemorrhage from the nose or intestine, no eruption, no cough. Quinine was given in twenty-grain doses in the morning,

when the temperature was the lowest, the bowels having been previously cleared out, but with apparently no beneficial effect. The fever disappeared at the end of four weeks, for three days, and then began again, but with greater severity, the morning temperature averaging 102.5° F., and the evening temperature 104° F. This second attack lasted also about four weeks. During the whole of the second attack she was kept on milk and Vichy. There was no delirium, no epistaxis, no eruption, and no enlargement of the spleen, and no diarrhœa. After this attack she remained free from fever about three weeks, and went up to a village on the Ante-Lebanon range, about six thousand feet above sea-level. Here the fever again returned, early in October, 1896, and has been persistent up to the present time – January, 1897. In December the fever began to change its character (while on board a steamer leaving Beirut), and there was an intermission each day instead of a remission. She also began to have a slight chill each day (sometimes a severe one), and almost always about the same hour. While in Switzerland, in December, she was given large doses of quinine, as much as ninety grains a day, but without benefit. Twenty grains a day by subcutaneous injection failed to give more than temporary relief. The voyage across the Atlantic, early in January, 1897, gave much benefit, and she has continued to improve daily since her arrival in America. The attack of fever at the present time only lasts a few hours, beginning about 2 P.M. and passing off about 6 P.M.

Since coming to New York she has taken quinine on several occasions on going to bed, and with apparent good results. Her menstruation during all these attacks has been fairly regular. Since October she has had almost constantly severe night-sweats. These were most severe in Montreaux, Switzerland, in December, 1896. They were, at times, so severe that she was obliged to change her clothing as often as three times during the night. During all these attacks she had a fairly good appetite, and seemed to digest her food with but little distress. When put on a pure milk-diet, or milk and Vichy, her fever was not affected, and she lost flesh and strength more rapidly than when on a more liberal diet.

The foregoing history was furnished by the patient's husband, a physician. He has been practising in Beirut, Syria, several years, and states that his wife's case is similar to others he has seen, the disease being known there as "Levant fever."

When I first saw her a careful examination failed to reveal evidence of lesion of any kind anywhere in the body. The patient has been seen repeatedly since that time up to the latter part of April, and has on each occasion shown elevations of temperature at some time in the day, usually in the afternoon up to early evening. The daily variations have differed somewhat. At first they were about 2°, and in the month of February they continued about the same; but in March, for a period of six days, the diurnal varia-

tions were 3°. In April a careful record of the temperature was kept for ten days at a time, at two different periods, and the variations were sometimes as much as 4°. When they were as great as this there would often be a subnormal temperature in the morning. Since the latter part of January she has been able to go about the city, and even make short trips out of town to visit friends. The improvement in her general condition has corresponded with the results of the examinations of the blood during this period, which have shown a continual improvement. The last examination of the blood was made on April 9th, and was as follows:

Red corpuscles	4,600,000
White corpuscles	9,200
Hæmoglobin	92 per cent.

Examination of the stained specimens showed the same parasite as herein described, but much less frequently. The red corpuscles were otherwise normal. The leucocytes were apparently normal, and the various forms present in normal relative proportions.

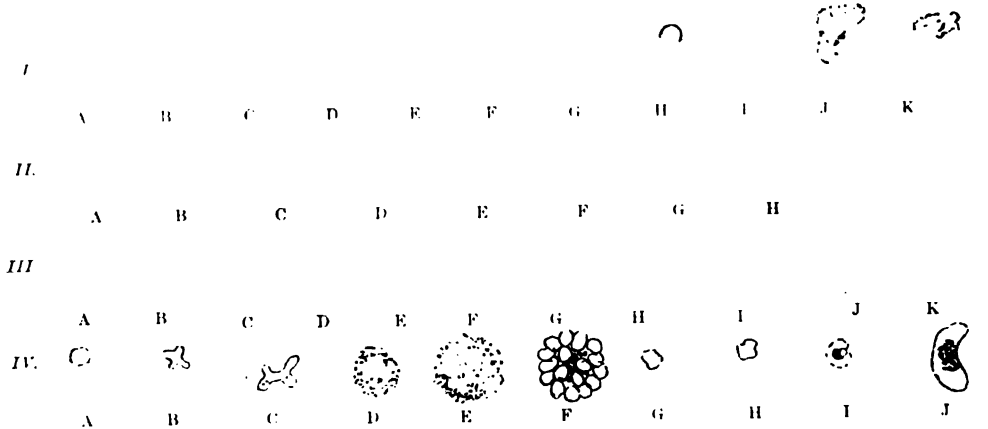
The blood examinations were made by Dr. John S. Billings, Jr., who has had much experience in such work.

Report on the examination of the blood.

January 14, 1897. Temperature 103 5° F.

Red corpuscles	3,740,000 per cm.
Leucocytes	20,200 "
Hæmoglobin	87 per cent.

Examination of fresh specimens showed the red corpuscles to be fairly normal. No variations from the normal in size or shape were observed. (Poikilocytosis and schizocytosis respectively.) No pallor of centre of corpuscles. A well marked leucocytosis was present. The corpuscles contained no blood pigment, nor was any observed free in the plasma The blood plaques were apparently normal. In a large number (about one-tenth) of the red corpuscles there were observed bodies resembling markedly the intracellular hyaline forms of the malarial parasite. Certain differences were observed, however. Fully one-half these organisms or parasites were much larger than the intracellular hyaline forms of the malarial organism, as seen in the tertian and æstivo-autumnal types of that disease. No pigmented forms were observed. The larger forms were central in position, and took up fully one-half or more of the red corpuscle. The smaller forms were amœboid, but never to the degree seen in the malarial organisms. The bizarre cross and chair forms, so common in tertian malarial fever, were never observed, nor the ring-like forms of æstivo-autumnal fever. These smaller forms were, as a rule, eccentric and peripheral. Their power of amœboid movement manifested itself in a slow change of shape from a circle to a square or five- or six-sided figure, and then back again. They move around within the red corpuscle, and in a few cases were seen to force out the cell-wall of the red corpuscle into a small knob-like projection (*c*). In two cases the organism



I. A to K. The parasite as seen in fresh specimens.
II. A to H. The parasite as seen in specimens stained with Ehrlich-Biondi triple stain.
III. A to K. The parasite as seen in specimens stained with eosin and methylene-blue.
IV. A to F. The parasite of malarial fever of the tertian type as seen in fresh specimens.
IV. G to J. The parasite of malarial fever of the aestivo-autumnal type as seen in fresh specimens

was seen to have partially escaped from the red corpuscle (*d*). These were probably not artefacts, as the corpuscles around were perfectly normal. The outline of these bodies was much fainter than that of an intra-cellular hyaline malarial organism. Nothing resembling the process of segmentation was observed, with the exception of one red corpuscle in which four of these organisms were seen, each one being amœboid (*e*). One specimen was ringed with vaseline and kept under the microscope for an hour, but nothing new was seen. No forms larger than two-thirds of the volume of the red corpuscle were seen. Both the forms which were observed in the act of escaping from the red corpuscle were of this size. It is just possible that this is a regular process, or that the corpuscles containing these larger forms remain within the spleen and segment there, as in the case of the organisms of æstivo-autumnal malarial fever.

Examination of dried specimens, hardened and stained by the various methods used in blood examination, showed these organisms to stain similarly to the malarial organism. The best results were obtained by hardening in equal parts of alcohol and ether for an hour, and staining with a dilute solution of gentian violet. No evidence of any nucleus was to be made out, even by using an apochromatic objective and high eye-piece. Nothing further was to be made out in the stained specimens than has been already described under the head of the fresh specimens.

The red corpuscles containing the organisms showed no variations from the normal in staining, but a comparatively moderate number of polychromatophilic red corpuscles were observed, none of which contained the parasite. A differential count of one thousand leucocytes in a specimen stained with Ehrlich-Biondi triple stain showed the leucocytosis to be due to an increase in the number of polynuclear neutrophilic forms, there being an absolute as well as relative diminution in the number of the small mononuclear forms. The eosinophilous forms were also markedly diminished in number, as we would expect to find in a case of fever of such long duration as the present one.

Polynuclears, 91.4 per cent.; large mononuclears, 5.3 per cent.; small mononuclears, 3.2 per cent.; eosinophiles, 0.1 per cent.

No abnormal forms of leucocytes or red corpuscles were observed. (Myelocytes or nucleated red corpuscles, respectively.)

No new forms of the organism nor any morphological characters not already described were observed in any of the subsequent examinations. A culture on blood serum from the blood showed no growth of any kind.

15*th*, 8.30 P.M. Temperature 100.2° F.

Examination showed the organisms were much fewer in number, the proportion being about one-half as many as were seen on the previous day.

17*th*, 12 M. Temperature 101° F.

The organisms in the blood were almost as numerous as on the 14th.

19*th*, 4 P.M. Temperature 102° F.

Result of the examination as on January 14th.

24th, 9 A.M. Temperature 98.5° F.

Very few parasites were observed in the blood, and all those seen were of the smaller variety.

27th, 12 M. Temperature 101° F.

Red corpuscles	4,240,000 per cm.
Leucocytes	12,800 "
Hæmoglobin	93 per cent.

Examination showed the parasites to be distinctly less numerous than they were at the same hour on January 17th—ten days previously. This coincided with the distinct improvement of the patient during that time. The range of the fever had been lower, and she was distinctly less anæmic, as shown by the increase of 500,000 per c.cm. in red corpuscles, and of 6 per cent. in the hæmoglobin. A differential count of the leucocytes showed that the number of the various forms had returned almost to their normal relative proportions.

Polynuclears, 81.4 per cent.; large mononuclears, 3.6 per cent.; small mononuclears, 14.8 per cent.; eosinophiles, 0.2 per cent.

The number of the eosinophiles still remains diminished, however.

February 5th, 2 P.M. Temperature 100.1° F.

Since February 1st the patient had been taking ten grains of sulphate of quinine—fifty-five grains in all. The number of organisms was fewer than at the same hour on other days, one being seen in about every two fields of the microscope.

We have here in the blood a parasite resembling somewhat the youngest forms of the organisms seen in the two types of malarial fever prevailing in this country. It differs from them in certain important particulars. It is found in the blood in the largest numbers during the height of the febrile paroxysm. In malarial fever the young intra-cellular hyaline forms of organism are not abundant until some hours after the height of the febrile paroxysm—*i.e.*, until sufficient time has elapsed after segmentation for the young parasite to penetrate the red blood-corpuscles. The time-cycle is shorter with this parasite than in the forms of malarial fever prevalent in this country. In the fevers of the tertian and double tertian (quotidian) type the time-cycle (*i.e.*, the time it takes the organism to go through all the stages of its development and begin anew) is about forty-eight hours. In æstivo-autumnal fever the time cycle is about thirty-six hours, and in quartan fever about seventy-two hours. This parasite is resistant to quinine, while the younger forms of the malarial organism are very susceptible to it. Other differences are the larger size of this parasite, its freedom from pigment, its comparatively feeble power of

amœboid movement, absence of segmentation, fainter outline and absence of the characteristic forms of the malarial organism as we know it in this country. (Bizarre forms, ring-like forms, crescents, etc.) The case could only have been confused with one of the æstivo-autumnal or fall type of malarial fever, as a case of tertian malaria would have shown the larger pigmented forms of the organism, and a case of æstivo-autumnal malarial fever of such long duration would, in all probability, show the so called crescentic bodies.

CHARACTERISTICS. In this case there was a period of fever lasting four weeks and followed by an interval of three days of freedom from fever. Then there was a second run of fever, more severe than the first, and lasting four weeks, the morning temperature being 102.5° F., and the evening temperature 104° F. This was followed by freedom from fever for three weeks, and then a recurrence, beginning October 1, 1896, and lasting persistently until January, 1897—indeed, until the latter part of April, 1897, the time when the patient was last observed. At first the fever was of a remittent type; later it changed to intermittent. It seems to have been resistant to quinine. No pigment was found in the blood plasma nor in the corpuscles. It should be stated, however, that no blood was taken from the spleen for examination. It was thought wise not to puncture the spleen, as the latter was not enlarged. There was no marked degeneration of the blood corpuscles. The attack has now lasted more than ten months. Since the patient's arrival in New York, although she has had fever to a greater or less extent every day, she has enjoyed a fair degree of health—has, indeed, constantly improved in her general health.

While it must be admitted that the organisms, as shown in the accompanying plate, resemble very closely some of the forms of malarial organisms, there are many features about the case which would suggest that it is not malarial in its origin. Observers in the Levant have looked upon this type of fever as malarial, notwithstanding its marked resistance to quinine; but the fact that there is no pigment found in the blood plasma or in the corpuscles; that it is resistant to quinine; that no marked degeneration of corpuscles is produced, such as we see in malarial fevers in this country, and no enlargement of the spleen, would suggest more than a doubt of its being of malarial origin. It

will be observed that although she had lived in a malarious region in Southern Iowa up to the time of her marriage, and that various members of her family there had suffered from malarial manifestations, she had never had any such manifestation until she went to Syria to live.

LITERATURE. A careful search through the literature of the fevers occurring in the Levant, or countries bordering on the Mediterranean Sea, shows the greatest confusion of ideas among the various observers. Should we judge by the nomenclature, we would say that these countries suffer from a larger variety of fevers than any other part of the world, for besides typhoid, typhus, and malarial fevers, which are all prevalent in these countries, mention is made of Malta, Neapolitan, Levant, Gibraltar, Rock, and Mediterranean fevers. No two articles on the same fever agree, for, where one man may be describing typhus fever, another may be describing malarial fever; and the same name is often used for different diseases. For instance, the attending physician of the case here reported stated that he has seen several such cases, and that it is known as Levant fever; but in the *Index Catalogue* of the Army Medical Library Levant fever is classified under the head of typhus fever. The bubonic plague is also sometimes known as the Levantine disease or plague, thus adding another source of confusion, so that we must be content with such reports as correspond to the case in question. Undoubtedly most of the cases of fever bearing the name of a given locality fall under the head of typhoid, typhus, or malarial fever. But that a fourth variety of continued fever occurs is well shown in the excellent articles of Bruce[1] and Hughes,[2] and it is to this variety of continued fever that the case here reported may probably be ascribed.

The articles of Bruce may be abstracted as follows: He saw at Malta many cases of what he terms "Mediterranean fever," presenting the following characteristics: It is a subacute, infectious, noncontagious disease, characterized clinically by fever, sweats, constipation, and frequent relapses. It is usually accompanied or followed by severe rheumatoid or neuralgic pains, with redness, tenderness, and swelling of the various joints. The spleen is large and soft. As the disease progresses, anæmia develops. The disease prevails during

[1] Bruce: Annales de l'Inst. Pasteur, 1893, vol. vii. p. 289.
[2] Hughes: Ibid., p. 628. Lancet, London, December 3, 1892.

the summer months. The mortality is not high, the death-rate being about 2 per cent. of all cases. There is general malaise, headache, etc., for eight to ten days, when the temperature rises gradually, taking three or four days to reach its maximum, after which it runs a course of remittent type, falling to 100° F. in the morning hours, and rising to 103° and 104° F. in the afternoon. The fever generally lasts about one month, the temperature gradually falling to normal, where it remains about three days, when the same course of events repeats itself. This is repeated three or four times, the patients being in the hospital for three months or more. The disease may last six months or a year. The fever is but little influenced by quinine or arsenic beyond the temporary antipyretic effect of large doses of the former. The plasmodium of malaria is not present; there are no rose-spots or tympanites; and on post-mortem the Peyer's patches are found to be unaffected. Bruce has found in the spleen a micrococcus (m. melitensis) which he holds to be the cause of the disease. Monkeys injected with cultures of this organism showed a typical rise of temperature and continued fever, lasting some months, and the micrococcus was found in the spleen and internal organs on autopsy.

Hughes confirms these statements of Bruce. He says the disease is characterized by intermittent waves of pyrexia of a remittent type —one to three weeks of fever, and two to three days' interval. In rare cases these remissions are so marked as to take the form of intermissions, with a sharp rise of temperature in the morning and a gradual fall at night. The disease does not confer immunity against a second attack, and several instances of typhoid following it were observed. Hughes also finds the m. melitensis constantly associated with the disease, but does not believe it to be the actual cause.

DISCUSSION.

DR. F. C. SHATTUCK: I would like to hear from Dr. Smith whether arsenic had any effect.

DR. SMITH: All forms of anti-malarial treatment were resorted to except phenic acid, and none of them gave any relief.

DR. GEORGE DOCK: Have the bodies described been numerous or few? I mean, what has been the usual proportion to the blood corpuscles?

DR. SMITH: They are fewer now than they have been in the last few weeks.

DR. DOCK: Hearing Dr. Smith's interesting paper and looking at his drawings, one must be struck by the absence of pigment in the supposed parasites. We remember that some of the Italian observers described organisms which go through their whole course of development without forming pigment; but even when this happens there are present in the blood pigmented parasites also, or at least pigmented leucocytes. In the latter case we must suppose the pigment-forming organisms develop in the internal organs. So that the entire absence of pigment in Dr. Smith's case offers a striking contrast to malaria. Another very striking difference is the absence of any indication of development and reproduction. Moreover, it will be noticed that in the colored drawings the bodies all show a uniform tint. Malarial parasites would show, at least in some specimens, more deeply stained areas; and as these are very important in all biological work, it would seem as if their absence here is not due to accidental choice of specimens by the artist. So the protozoon nature of the bodies seems to me to be very uncertain. Dr. Smith's statements that the bodies are found in very small numbers, one or two in a preparation, and only in the febrile access, suggest another explanation. It will be remembered that in the early days of our knowledge of malarial parasites inexperienced observers, otherwise familiar with the microscope, indeed found in the blood, especially in the various kinds of fever, bodies very much like those now described. From the observations of Maragliano and others it seems that these are bits of protoplasm, either from red or white corpuscles. I have found such bodies not infrequently, and although an inspection of Dr. Smith's specimens in fresh blood might cause me to change my mind, I doubt whether they can be looked on as the cause of Levant fever.

AN EPIDEMIC OF CEREBRO-SPINAL MENINGITIS.

CLINICAL REPORT, BY FRANCIS H. WILLIAMS, M.D., OF BOSTON.

I DESIRE to outline briefly the experience we are having at the Boston City Hospital with an epidemic of cerebro-spinal meningitis.

The first case entered the hospital December 30, 1896, and nearly all the cases since then have been in the service of Drs. Withington and V. Y. Bowditch and in my own. The records of the hospital from 1880 to December 30, 1896, include thirty-nine cases, with a mortality of 59 per cent. From the latter date to June 1st there have been forty-seven cases[1] (see appended table), forty-two of which entered in March, April, and May—that is to say, during the past five months there have been more patients with this disease in the hospital than in the previous seventeen years.

The tabulation of these forty-seven cases by localities, made by Dr. C. B. Dunlap, shows that one part of the city has not been more affected than another. The patients have been youths and adults, as the children have been sent to the Children's Hospital, and the form of the disease has been very severe. It has been characterized by sudden onset, with an average duration of about thirteen days in the fatal cases, and the very high mortality in forty-seven, the whole number of cases, of a little over 72 per cent.

The prominent symptoms have been intense headache, delirium, a stiffness of the muscles of the back of the neck, retraction, and stupor; in some cases there have been diplopia, strabismus, deafness, and vomiting; in eleven cases herpes labialis; in seven cases some form of eruption, but this does not justify the name of spotted fever which is sometimes given to this disease. In twelve cases a blood-count was made, and in most of these there was leucocytosis. The serum-test for typhoid fever was tried in eight cases, and found

[1] To make this report more complete I have included the cases that entered during May.

Date of entrance.	Name.	Age.	Duration.	Prodromata.	Headache.	Neck.	Vomiting.	Drowsiness.	Delirium.	Coma.	Convulsions.	Eyes.
1896 Dec. 30	Frank H.	23	3 days	Chill; took care of child who died of meningitis.	Frontal	Stiff.	x	...	x	...	...	.....
" 31	Geo. F.	26	1 day	Found unconscious.	...	Retracted.	...	...	...	...	x	Strabismus, cont. pupils, slight neuritis.
1897 Jan. 2	Jos. P.	27	5 days	.....	x	.....	...	...	x	x	...	.....
Feb. 8	John L.	49	1 day	Alcoholic excess.	...	Retrac.	...	...	...	x	...	.....
" 10	Wm. H.	40	18 "	Headache.	x	Retrac.	...	...	x	...	...	.....
Mar. 5	John F.	31	14 "	Alcoholic. Malaise.	x	Retrac.	...	...	...	...	...	.....
" 6	Mike M.	17	10 "	.....	x	Pain, retrac.	x	...	x	...	...	Diplopia, ptosis, double optic neuritis.
" 9	C. H.	25	1 day	Found unconscious.	x	Retrac.	...	...	...	...	...	.....
" 10	Alfred B.	...	6 w'ks	Headache, occip. and cerv.	x	Slight retrac.	...	...	x	...	...	Slight optic neuritis.
" 10	Richard S.	23	10 days	Headache,	x	.....	x	...	Violent.	...	...	.....
" 11	Sophie M.	17	2 "	Chill; headache.	x	Pain.	x	...	x	...	...	Diplopia, strabismus, ptosis.
" 11	Frank R.	23	2 "	Alcohol, stupid.	...	.....	x	...	x	...	...	Strabismus.
" 17	Celia McC.	25	4 "	Indef. pain, vomiting.	x	Tender.	x	x	...	...	...	Nystag., diplopia.
" 18	S. P.	33	18 "	.....	x	Stiff, retrac.	...	...	x	...	...	.....
" 19	Chas. K.	15	25 "	Headache.	...	.....	x	x	...	...	x	Strabismus, nystag.
" 20	Porter A.S.	37	7 "	Headache, gen. pains.	...	.....	x	...	x	...	...	.....
" 25	Jessie E.	17	4 "	Headache, gen. pains.	x	Pain, retrac.	...	...	x	x	...	.....
" 30	Martin C.	19	5 "	Headache.	x	Stiff, retrac.	x	...	x	...	...	Sl. optic neuritis.
" 30	Thos. T.	27	8 "	Malaise, headache, delirium.	...	Stiff, retrac.	...	...	...	...	...	Strabismus
April 1	Mertie K.	33	3 "	Vomiting, occip. headache	x	Stiff.	...	...	x	x	...	Strabismus
" 5	Kate G.	15	1 day	Irritable.	x	.....	x	...	x	...	...	Strabismus
" 5	Mike M.	35	2 days	Pain back and legs; headache, delirium.	x	Retrac.	x	...	...	...	...	.....
" 6	Alex. McC.	...	?	.....	...	.....	...	x	...	...	...	Nystag.
" 17	Art. McK.	24	1 day	Sorethroat, headache.	x	.....	x	...	...	x	...	.....
" 17	John S.	24	3 days	Headache.	x	Stiff.	x	...	x	...	...	.....

Ears.	Paralysis.	Eruptions.	Tâche cerebrale.	Widal's serum reaction.	Herpes.	Pneumonia.	Leucocytosis.	Autopsy.	Lumbar puncture.	Died.	Recovered.	Remarks.
.....	.....	.....	x	0	...	...	11th dy. 16,500	...	.....	.....	Jan. 26	
.....	.....	.....	...	...	...	...	.....	...	.....	Jan. 4		
.....	.....	.....	...	...	...	...	2-5th d. 9,000	x	.....	Jan. 5		
.....	.....	.....	...	...	...	x	.....	x	.....	Feb.10		
.....	Right side.	.....	...	...	...	...	.....	x	.....	Feb.17	.....	Paralysis day before death.
Tender mastoids	.....	.....	...	0	...	...	18,800	...	March 13. dry tap.	.....	Apr.10	
Deaf in left ear, secondary to mening.	.....	.....	x	...	...	...	Mar. 8, 8,200 Mar. 11 16,000 Mar.15, 22,000	...	March 15, 3ij slightly turbid, no pus, mono leucocytes.	Mar.21	.....	Cephalic cry.
.....	.....	.....	...	...	...	...	.....	x	.....	Mar.21	.....	Musc. rig., struggling, slept after puncture.
.....	.....	.....	...	...	...	...	.....	...	March 10, 3ij turbid. diplococci.	.....	Apr.10	Tenderness over spine.
.....	.....	.....	...	0	...	...	.....	...	.....	Apr. 6	.....	Tuberculin, no reaction.
.....	.....	.....	x	...	..	...	4th dy. 31,000	...	March 14. 3ij turbid, diplococci.	Mar.16		
.....	Tongue to left.	.....	...	0	...	...	7,490	...	March 20, 3ij clr. ster.	.....	Apr. 3	
.....	3d-6th nerve.	.....	...	0	...	...	.....	...	2 dry taps.	Apr. 2	.....	Epistaxis.
.....	.....	.....	...	...	...	...	.....	...	March 21. pus cells.	Mar.22		
.....	.....	Purpuric spots on r. knee, wrist, forearm, elbows.	x	...	x	...	.....	...	March 20, 3j turbid, diplococci.	Mar.22		
.....	.....	.....	...	0	...	...	Mar. 24, 14,000	...	March 23, 3iv turbid.	.....	May 17	Well, mental symptoms.
.....	.....	.....	...	...	...	...	.....	x	.....	Mar.26		
Deafness from mening.	.....	.....	...	0	x	...	9,350	...	.....	.....	Apr.19	Well.
.....	.....	.....	...	...	x	...	April 1, 21,600	...	April 1, turbid.	Apr. 2		
.....	.....	.....	...	...	...	...	.....	...	April 3, no fluid.	Apr. 5		
.....	.....	.....	...	...	...	...	.....	x	.....	Apr. 5		
.....	.....	.....	...	...	...	...	.....	...	April 6, 3ij purulent fluid.	Apr. 6		
Tender mastoids.	.....	.....	...	...	...	...	.....	x	April 9, dry tap.	Apr. 9		
.....	.....	.....	...	...	...	...	.....	x	.....	Apr.17	.....	Unconsci's, restless
.....	.....	Petechiæ l. elbow, buttocks.	...	0	...	...	.....	x	Sterile.	Apr.23		

Date of entrance.	Name.	Age.	Duration.	Prodromata.	Headache.	Neck.	Vomiting.	Drowsiness.	Delirium.	Coma.	Convulsions.	Eyes.
1897 Apr. 18	Pat. O'B.	26	3 days	Severe headache, vomiting.	x	Stiff.	...	...	x	x	...	Ptosis.
" 18	Geo. K.	50	8 "	Delirium.	...	.....	...	...	x	...	...	Optic neuritis, strabis. no react'n.
" 21	Pet. McG.	29	4 "	Chill, headache, delirium.	x	Retrac.	...	...	x	...	...	.....
" 21	Chris. D.	19	8 "	Headache, chill.	x	Rigid.	x	...	x	...	...	.....
" 22	Emma N.	36	10 "	Chill, pain in back, headache.	x	Stiff.	...	...	x	...	...	.....
" 22	Daniel M.	28	4 "	Headache, pain in abdomen, delirium.	...	Stiff, retrac., opistho tonos.	...	...	x	...	...	.....
" 26	Geo. W.	28	2 "	Headache, vomiting.	...	Rigid, tenderness.	x	...	x	...	...	Conjunctivitis.
" 30	James W.	27	11 "	Sorethroat, headache, vomiting.	...	Retrac. rigidity	...	...	x	...	...	Sl. nystag. conjunctivitis.
May 4	James C.	16	3 "	Headache, vomiting, vertigo.	x	Retrac. tenderness neck and back.	...	...	...	...	...	.....
" 7	Andr'w H.	27	4 "	Pain in legs, vomiting, nose bleed.	x	Stiff.	...	...	x	...	...	Ptosis.
" 12	Thomas D.	40	3 "	Headache, sorethroat.	x	Pain, tender.	...	...	x	...	...	External strabis. r.
" 14	CassieMcG.	23	3 "	Headache, pain in neck.	x	Stiff, pain.	...	x	...	...	...	.....
" 17	John S.	27	7 "	Pain in neck and legs, headache.	x	Pain, stiff.	x	...	x	...	...	.....
" 5	Thomas S.	35	5 "	Pain in back, headache, chills.	x	Stiff.	x	...	...	...	...	.....
" 17	Henry H.	58	3 "	Headache, vomiting, abd. pain.	...	Stiff, retrac.	...	...	...	x	...	.....
" 21	Everett M.	26	14 "	Pain in back, headache.	x	Stiff.	x	...	...	...	...	.....
" 22	Con'r O'B.	25	2 "	Headache, gen. pains	...	Stiff.	...	...	x	...	...	Slight strabis.
" 13	Julius E.	58	3 wks	Drowsiness; indef. hist.	...	Tend'r, stiff.	...	...	x	...	...	Ptosis, left pupil smaller, neither react.
" 24	Jane O'C.	13	2 days	Pain in back.	...	Retrac.	x	x	x	...	..	.....
" 30	Wm. B.	17	4 "	Frontal headache.	x	Slight retrac. stiff.	x	...	x	...	...	Internal strabismus.
" 30	John McC.	35	.....	.....	...	.....	...	...	...	...	...	.....
" 31	Eugene L.	37	3 wks	Vomiting, headache, pain in small of back and legs.	x	Stiff, rigid.	...	x				

x = yes. o = negative.

Autopsies, 15. Died, 34.

Ears.	Paralysis.	Eruptions.	Tâche cerebrale.	Widal's serum reaction.	Herpes.	Pneumonia.	Leucocytosis.	Autopsy.	Lumbar puncture.	Died.	Recovered.	Remarks.
.....	.....	Macules,	...	...	...	...	.....	...	Small am't, clear, sterile	.....	June 26	
.....	.....	.....	...	...	...	...	.....	...	April 16, diplococci.	Apr. 20		
.....	.....	.....	...	...	...	...	.....	x	April 22, slv turbid, diplococci.	Apr. 23		
Pain over mastoids	.....	Macules, pediculi.	...	...	x	...	.....	...	Turbid fluid.	.....	June 8	
.....	.....	.....	...	...	x	...	Apr. 30, 24,500	...	Diplococci.	.....	June 5	
.....	.....	.....	...	...	...	...	Apr. 27, 11,400	...	3 times. 1 pus cells, 2 diplococ, 3 sterile.	.....	May 22	
.....	.....	Petechiæ over whole body marked.	...	...	...	...	.....	x	April 28, few drops bloody fluid.	Apr. 29		
.....	.....	.....	...	...	...	...	.....	...	May 2, pus cells.	May 8		
.....	.....	.....	...	...	x	...	.....	...	.....	May 29		
.....	Compl. r.-sided paral.	.....	...	...	x	...	.....	...	May 9, 60 cc. turb. diplococci.	May 29		
Deafness.	.....	.....	...	...	x	...	.....	...	May 13 and 19, dry taps.	May 19		Reflexes absent.
.....	.....	.....	...	...	...	...	.....	...	May 15, diplococci.	May 15	.....	Endocarditis.
.....	.....	.....	...	...	x	...	.....	...	May 20, diplococci.	June 3		
.....	.....	Slight petechiæ	...	...	x	...	.....	...	May 7, dry tap.	.....	May 22	
.....	Right leg.	.....	...	...	...	...	.....	x	May 18, p.m. dip.	May 18		
.....	.....	.....	...	...	x	...	.....	...	May 22, dry tap.	.....	June 26	
.....	.....	.....	...	...	...	...	May 25, 32,000	x	May 24, diplococci.	May 25		
.....	.....	....	...	...	...	...	.....	x	....	May 19	.....	Hydrocephalus.
.....	.....	.....	...	...	...	...	.....	...	.....	May 26		
.....	.....	.....	...	...	...	...	.....	...	May 31, diplococci.	May 31		
.....	.....	.....	...	...	...	x	.....	...	Diplococci.	.....	June 26	
								x	.....	June 6		

x = yes. o = negative.

Recovered, 13. Total, 47.

to be negative in all. Lumbar puncture was done in thirty-two cases, and judging from these this puncture does no harm, and it readily establishes the diagnosis when fluid containing pus and organisms is found. In the seven cases in which I performed the operation it yielded a positive result in all.

The operation, under strict antiseptic precautions, is readily done by using a small trocar to tap the sac surrounding the spinal cord, and drawing off some of the fluid; the point of insertion is between the third and fourth lumbar vertebræ. I have usually chosen a point slightly lower than the lowest part of the spinous process of the second lumbar vertebra, and one inch outside of it, and inserted a small-sized trocar, somewhat downward and inward, to a depth of rather more than two inches. I have always used a trocar instead of a needle, as the latter is liable to be bent or broken off, and is too small to allow the thick pus that is present in some cases to flow through it easily.

The lumbar puncture is very serviceable for diagnosis, as often there is no history and the symptoms may be few; it may also relieve pressure temporarily. That there is pressure is shown by the fact that the fluid is apt to squirt out at first with some force; and sometimes two ounces may be readily withdrawn.

The diagnosis has been established in more than half of these forty-seven cases either by examination of the fluid obtained by lumbar puncture or by autopsy.

The present treatment of the disease is wholly unsatisfactory; but the fact that we have the means of making an early diagnosis in many cases, and that the organism is not a robust one, and seems to be short-lived in the body, offers the hope that better treatment may soon be found.

Pathological Report, by W. T. Councilman, M.D.

In 1886 Weichselbaum described in the *Fortschritte d. Med.* a peculiar form of micrococcus, resembling the gonococcus, which he found in six cases of acute cerebro-spinal meningitis. When these six cases appeared the disease was not prevailing in Vienna in an epidemic form, although there was a slight epidemic in Maiberg. The organism described by Weichselbaum was a diplococcus, occur-

ring almost solely within the cells. It grows best on agar, the growth only appearing in the first cultures after forty-eight hours, although in the second cultures it may appear in twenty-four hours. It forms a grayish-white, rather viscid growth, and at the edge the colonies appear to be formed of smaller confluent masses. The organism does not grow at room temperatures, and soon loses its vitality so that new cultures must be made every two days. The microscopic examination of the cultures shows the organism single, in pairs, and in fours. Both in the cultures and in the tissues it decolorizes in Gram and stains best in Lœffler. It was not easy to recognize in sections of the meninges, and but few were found in most cases. Inoculations were made on mice, guinea-pigs, rabbits, and dogs. Subcutaneous inoculations were successful in no cases. White mice proved the most susceptible and died in from thirty-six to forty-eight hours after inoculation in the pleural or peritoneal cavity. In guinea-pigs and rabbits inoculation into the pleura or peritoneum was not always fatal, and there was a sero-fibrinous exudation in the serous cavity inoculated. The animals died in from twenty-four hours to four days. He produced meningitis and encephalitis in dogs by inoculating them into the meninges. He regarded this organism as one cause of acute cerebro-spinal meningitis, and called the organism the micrococcus intracellularis meningitidis.

Goldschmidt (*Centralblatt f. Bacteriologie*, 1887, No. 22) found the organism in a case of acute cerebro-spinal meningitis, and obtained the same results on inoculation which Weichselbaum obtained.

In 1895 (*Zeitschrift f. Hygiene*, vol. xix; "Zur ætiologie der Cerebrospinal epidemica") Jaeger described the Weichselbaum diplococcus in twelve cases of epidemic cerebro-spinal meningitis in the troops in Stuttgart. His description agrees essentially with that of Weichselbaum, with the exception of stating that a capsule was sometimes found around the cocci, and that cover-slips made from the cultures stained with Gram. In cultures he found there was considerable tendency for the organism to grow in the streptococcus form. He calls attention to the slight character of the exudation in the meninges in most cases. The number of the organisms found varied with the extent of the exudation, being most abundant in

those cases where the exudation was most marked. In only two cases were sections of the brain made, and in these the organisms were found in small numbers.

Heubner ("Zur ætiologie und Diagnose des epidemischen Cerebrospinal Meningitis," *Deutsche med. Wochenschrift*, No. 27) found the organism in the fluid obtained by lumbar puncture in nine cases of the disease. In six cases the diagnosis so made was confirmed by autopsy. He injected cultures of the organisms into the lumbar canal of animals, and produced the disease in goats, which he says are subject to meningitis.

Kister ("Ueber den Meningococcus intracellularis," *Centralblatt f. Bacteriologie*, 1896) obtained the organism from the fluid of spinal puncture in two cases. He found some difficulty in growing it in the ordinary media, and the growth was best in blood-serum agar. Subcutaneous inoculations of animals were without result, but animals inoculated in the pleura or peritoneum died in from four to six days.

Petersen ("Zur Epidemiologie der epidemischen Genickstarre," *Deutscher med. Wochenschrift*, 1896) investigated an epidemic of cerebro-spinal meningitis which appeared in Berlin in 1895 and 1896. In twelve cases which were autopsied he found the diplococcus in the fluid of the spinal canal.

Furbringer ("Todliche Cerebrospinal meningitis und akute Gonorrhöe," *Deutscher med. Wochenschrift*, 1889) found the diplococcus intracellularis in an individual who had acute gonorrhœa at the same time. The two organisms were so similar in appearance that he thought they might be the same, but cultures showed the difference.

There has been abundant confirmation of the original observations of Weichselbaum, and nothing of importance has been added to his description. All observers have agreed with him in the description of the organism, with the exception of Jaeger, who describes a capsule, and says that the organism in cover-slips made from cultures retains its color when treated with Gram. They all find that growth is best on agar and at a temperature of 35°–37° C. Subcutaneous inoculations are without effect, and in general no animal shows a high degree of susceptibility even when inoculated into the pleura or peritoneum. Inoculation in the serous cavities produces a sero-

fibrinous exudation, and the organisms are found in small numbers in the pus cells. Acute meningitis has been produced in dogs by inoculations of the meninges (Weichselbaum), and in goats by injecting cultures into the spinal canal (Heubner). In this way the causal connection between the organism and the disease has been shown. There has been a further agreement between the observers that the organism is found in the epidemic form in contradistinction to the sporadic forms. In many cases acute nasal catarrh has been observed at the same time and the same organism found in the nasal secretion and in the sinuses. It has been generally believed by them that infection of the brain takes place through the nose.

The only other organism which has been found with any degree of constancy in acute cerebro-spinal meningitis has been the pneumococcus. This has been found in more than 60 per cent. of all the cases investigated.

Leyden (*Centralblatt f. klin. Med.*, 1883), Senger (*Arch. f. Experimentel Pathologie*, 1884), Fraenkel (*Deutscher med. Wochenschrift*, 1886, and *Zeitschrift. f. klin. Med.*, vol. xi.), Foa and Bordoni Uffreduzzi (*Deutsche med. Wochenschrift*, 1896), Senger (*Arch. f. Experimentel Pathologie*, 1886), and others have described cases of acute cerebro-spinal meningitis in which the pneumococcus alone was found. It has been generally assumed that the organism described by Bonome (Ziegler's *Beitrage*, 1890), which he obtained in an epidemic of cerebro-spinal meningitis which appeared at Padua, was identical with the pneumococcus. The results of his inoculations speak in favor of this, but some of his descriptions might apply to the Weichselbaum organism.

Flexner and Barker (*American Journal of the Medical Sciences*, 1894) describe an epidemic of cerebro-spinal meningitis in Lonaconing, Maryland. They made two autopsies, and the cultures and inoculations from one were sterile. In the other there was a feeble growth of diplococci. Inoculations of animals both from the tissues and from the cultures were negative. Cover-slip examination showed numerous diplococci, both enclosed in the pus-cells and free. On histological examination of the exudation there was little fibrin. Cover-slips made from the brain showed lancet-shaped diplococci in capsules, sometimes free and sometimes enclosed in cells. Sections of the tissues stained with Gram and Weigert show lanceolate diplo-

cocci in the cells. The description which the observers give of the organism shows that it must have been the pneumococcus, although the character of the lesions and the results of the inoculation would speak rather in favor of its being the Weichselbaum organism.

This is the most extensive epidemic of cerebro-spinal meningitis which has been attributed to the pneumococcus. It is greatly to be regretted that so little opportunity for a thorough investigation of the epidemic was given.

It can be easily understood that a variety of organisms may produce acute meningitis if they find entrance in the meninges. This may take place by traumas, by extension to the meninges of a pathological process in the vicinity, by metastitis, or by primary infection. Not only the pus organisms, but a variety of others have been found.

On examining the cases of meningitis which have occurred at the Boston City Hospital in the last three years and up to the beginning of the present epidemic, we have found the pneumococcus to be the most common organism met with. The most frequent cases of meningitis have been those of extension from the middle ear with or without thrombosis of the lateral sinus. In seven of these cases the streptococcus was found four times; the staphylococcus once, and the pneumococcus twice. In four cases of acute meningitis with acute croupous pneumonia, two; endocarditis one; acute bronchitis and broncho-pneumonia, one, the pneumococcus has been found, the infection of the meninges being apparently secondary. Only two cases of acute meningitis due to pneumococcus without primary infection elsewhere have been found.

In the past six months we have had in the hospitals of Boston a number of autopsies in which the diplococcus intracellularis has been found. The autopsies came from the Boston City Hospital, the Massachusetts General, the Children's Hospital, and from private cases. At this time the disease may be said to be prevailing in Boston in an epidemic form.

The first case in which the Weichselbaum organism was probably, though not certainly present, occurred in June, 1896:

CASE I.—A. B., aged twenty years; over the pia arachnoid in all parts of the brain, but chiefly marked over the convexity over both hemispheres, there is a comparatively thin fibrino-purulent exudation; thrombosis of the lateral

sinuses. The cultures of the brain contained a number of contaminating organisms, but among them there were a few colonies of biscuit-shaped diplococci. The cover-slips made from the brain showed flattened diplococci in the pus-cells. In the report of the cultures it is expressly stated that the organisms were flattened and not elongated as the pneumococci. At that time, owing to a press of work in the laboratory, the organisms were not further investigated.

CASE II.—I. E., March 26, 1897. The convexity of the brain shows a yellowish infiltration more marked along the course of the larger bloodvessels, extending down into the fissure of Sylvius, and to a slight extent to the base of the brain. In the white matter on the right side outside of the basal ganglia were two irregular patches about 1 cm. in diameter, studded with punctate hemorrhages and surrounded by a yellowish zone which faded off into the white matter. In the optic thalamus on the right side about the centre was a small, reddish softened area, 5 mm. in diameter. On section the gray matter, to some extent on the right side and to a larger extent on the left, showed numerous small hemorrhages, with some softening of the surrounding brain-tissue. The dura of the cord was distended with a thin, purulent fluid. The meshes of the pia extending down over the cauda equina were infiltrated with a yellowish exudation. The vessels of the cord were injected. Smears from the pus of brain and cord show many pus-cells, some of which contain diplococci, flattened and growing in pairs and tetrads. There are also colonies of streptococci. The diplococci decolorize in Gram, the streptococci do not. In the brain there is an abundant growth of diplococcus colonies; no streptococci.

CASE III.—A. McC., aged fifty-five years. Over the convexity of the brain, chiefly along the vessels, there is a yellowish, gelatinous, purulent exudation, much more abundant on the right side and along the fissure of Sylvius. Over the base of the brain, extending up over the cerebellum, the greatest amount of the exudation is found, being in places over ½ cm. thick. Cover-slips from the brain and cord showed many diplococci, both free and in pus-cells. Those from the cord were especially abundant, often arranged around the nucleus and completely filled the cells. These diplococci stained with Loeffler and were decolorized by Gram. In the right tonsil there were two small ulcerations, and the follicles were filled with muco-purulent material. Cover-slips of the pus showed organisms identical morphologically with those obtained from the brain and cord, and were decolorized with Gram. In the lungs there were broncho-pneumonia and gangrene. Cultures from the meninges gave a pure growth of the diplococcus.

CASE IV.—W. H., aged thirty years. On the left side of the brain, involving the fissure of Rolando, extending over the entire base and over the upper surface of the cerebellum, there is a fibrino-purulent exudation. An exudation of the same sort is found in the meninges of the cord, particularly along the posterior surface. Cultures of the cord were sterile. In the cultures from the brain there were numerous small, whitish colonies. Micro-

scopically, these appeared as flattened diplococci, often arranged in small chains of three to five and in small groups. They decolorized with Gram.

CASE V.—J. E., aged eight years. Over the meninges of the convexity of the brain on both sides there is an abundant fibrino-purulent exudation. This extended down on both sides, involving the fissure of Rolando, and over the entire base of the brain and upper surface of the cerebellum. The meninges of the cord showed the same condition particularly marked in lumbar portion of the cord. In places the exudation was 3–5 mm. in thickness, and so dense that it could not be removed with the needle. Cover-slips showed a small number of diplococci in the pus-cells. They were flattened or arranged in pairs or tetrads, and decolorized with the Gram stain. Cultures from both the brain and cord showed a small number of opaque, grayish-white, viscid colonies. No contaminating organisms.

CASE VI.—Child, aged eight years. On removing the dura the surface of the brain on the left side showed an infiltration of the meshes of the pia with a yellow, opaque exudation thick enough to hide the convolutions beneath, most marked along the course of the bloodvessels. On the right side the exudation was much more serous in character and translucent, so that the brain-tissue could be easily seen. The exudation was the thickest along the longitudinal fissure on both sides, and extended about half-way down to the corpus callosum. At the base the exudation was most marked on the right side, particularly in the fissure of Sylvius. A considerable amount of the exudation was found just posterior to the optic commissure. Little was present about the cerebellum, the vessels of which were infected. It was found difficult to remove the exudation even with forceps; the serous portion flowed out easily, but the cells were held in a tough mass of fibrin. Both lateral ventricles contained a cloudy fluid, and in the posterior cornua there was a considerable collection of soft, purulent material. The meshes of the pia over the cord were infiltrated, particularly on the posterior surface, by an abundant yellowish exudation, which completely hid the cord itself. The inner surface of the dura of the cord was pinkish in color, due to injection. Considerable cloudy fluid escaped from the dura of the cord when it was opened. Microscopic examination of the exudation in the meninges showed short, broad diplococci, which decolorized in Gram, in small numbers, usually in the pus-cells. Cultures showed characteristic growth of the diplococcus intracellularis.

CASE VII.—J. S., aged thirty years. There was faint cloudiness along the bloodvessels over the convexity of the brain on both sides. At the base of the brain there was abundant yellowish, fibrino-purulent exudation in the pia. This was most abundant along the seventh and eighth nerves, and extended along them into the foramen. The lateral ventricles dilated and contained serous fluid, with a thick, soft, yellowish material in the posterior cornua. The pia of the cord showed the same sort of exudation in smaller amount. In the lumbar cord it was abundant posteriorly, and a mass of the exudation lay on the surface of the pia. Cover-slips and cultures showed the diplococcus intracellularis.

CASE VIII.—In this case the brain could not be examined. Along the cord there was a yellowish, thick exudation, and in the spinal canal there is considerable yellowish, cloudy fluid. Cover-slips and cultures showed the diplococcus intracellularis.

CASE IX.—(The notes of Cases IX. and X. were given me by Dr. Wright from the Pathological Laboratory of the Massachusetts General Hospital.) Body of a young man, well developed. The pia-arachnoid of convexity and base extensively infiltrated with a yellowish, cloudy fluid. In the ventricles a moderate accumulation of cloudy fluid containing yellow flocculi. On the meninges of the cerebellum, yellow, fibrino-purulent flakes. In the dural sac of spinal cord about 10 c.c. of cloudy fluid. Moderately marked fibrino-purulent exudation in the pia in the dorsal region of the cord.

Ecchymoses of pericardium. Œdema and congestion of lungs. Fatty metamorphosis of liver.

Bacteriological report. Direct examination of the exudate in the meninges, both of the brain and cord, shows more or less numerous diplococci, often inside of leucocytes. These cocci are composed of paired hemispheres and are decolorized by Gram's method.

Cultures on blood-serum. Two cultures from the exudate in the meninges of the cerebral cortex, one from the exudate on the cerebellum, one from the exudate on the spinal cord, and one from the fluid of the left lateral ventricle, all gave numerous colonies of the diplococcus intracellularis. With the exception of one culture from the cortex, and that from the spinal cord, this organism was not accompanied by other bacteria.

CASE X.—Body of a female child. Acute cerebro-spinal lepto-meningitis. Exudation along the vessels of the pia of convexity and small in amount. No accumulations of fluid at base nor in ventricles. In left optic thalamus a few very small hemorrhagic areas of softening. Disseminated ecchymoses in white matter of cerebral hemisphere. In the dural sac of the spinal cord a small amount of cloudy fluid and some fibrino-purulent exudate on pia.

Acute lobar pneumonia. Acute lymphadenitis of mesenteric lymphatic glands. No suppuration of middle ears. Superior portion of nasal cavity shows nothing except a doubtful redness of the mucous membrane.

Bacteriological examination. Direct examination by cover-glass preparations shows diplococci, often inside of leucocytes, in the exudate in the meninges of the brain and spinal cord. They are present in variable numbers.

Cultures on blood-serum. Four cultures from the cortical exudate all show colonies of the diplococcus intracellularis in variable numbers and in pure culture. Numerous colonies of the same organism also developed in the cultures from the meninges of the base of the brain and from the exudate in the dural sac of the spinal cord. In the latter cultures there also developed some colonies of what were probably the bacillus coli communis.

The culture from the pneumonic portion of the lung, on the blood-agar of Pfeiffer, yielded a somewhat mixed growth, in which the prevailing organism was the diplococcus intracellularis, as was shown by subcultures. A culture

from the mucous membrane of the superior portion of the nasal cavity showed the presence of the diplococcus intracellularis along with other bacteria. The coccus was isolated and studied in pure cultures.

Lumbar Puncture. The organisms were obtained from nineteen out of twenty cases of lumbar puncture made at the City Hospital, and in thirteen out of fifteen cases at the Children's Hospital. I am indebted to Dr. Wentworth for the notes on the latter. The cultures in eleven of the City Hospital cases were sterile, and in five of these a small amount of perfectly clear fluid showed the cases to be either very late cases of meningitis or some other disease. Of the other six cases, in four pus-cells were found, but the cocci were present neither on microscopic examination nor in cultures. One of these cases died, and at the autopsy a typical meningitis was found with considerable numbers of diplococci in the exudate in the brain and cord. In one case the organisms were found on the microscopic examination, but failed to grow in cultures. In two of the negative cases the puncture was made after death, permission for an autopsy not being given. The larger number of positive results obtained in Dr. Wentworth's cases in the Children's Hospital is probably to be accounted for by the fact that these cases were observed much earlier than those in the City Hospital. In the positive cases the character of the fluid varied from an almost clear serous fluid up to almost pure pus. In only one case did it contain any considerable amount of blood. Dr. Wentworth's cases show a difference in character of the fluid depending on the duration of the disease. In one case the fluid at the first tapping, ten days after the onset of the disease, was clear, without sediment or organisms. The temperature at this time was normal. Seven days later, during an exacerbation of the disease with rise of temperature, the patient was tapped a second time, and the fluid contained pus-cells and diplococci. In a second case in which three lumbar punctures were made the fluid showed a constantly diminishing degree of turbidity, though all showed the organisms. An admixture of any considerable amount of blood in the fluid withdrawn is probably accidental. On microscopic examination of the fluid in the positive cases it is found to contain variable numbers of pus-cells (polynuclear leucocytes), a very few red blood-corpuscles, and a few large epithelioid cells which occasionally contain enclosed pus-cells. The organisms are present in variable numbers,

and chiefly in the pus-cells. The cells sometimes contain a single pair, or may be filled with them. I have never been able to demonstrate them in the nucleus, although they may lie against and indent this. They are generally in pairs, although occasionally tetrads may be seen. It would be easy to mistake them in cover-slips of the exudation for gonoccoci, but they differ from these in the marked variability in size which they show and in their less distinct stain. They never stain so vividly as do the nuclei of the cells.

The Pathological Lesions. The amount of the exudation varies, and is generally more abundant at the base of the brain and in the cord than over the convexity. In the slightest cases only a faint turbidity in the sulci and along the course of the vessels over the convexity may be found. It may or may not be accompanied by serous exudation. In one case there was a large serous exudation in the meninges. The exudation is never found on the surface of the pia in the brain, but may be found in considerable amount on the surface of the pia in the lower portion of the spinal canal. It is usually whitish yellow in color. In two cases it was found in the greatest amount on each side of the longitudinal fissure, and in one place here was 5 mm. in thickness. The microscopic examination in all cases showed about the same condition. The amount of fibrin varied and was most abundant where the exudation was thickest. In all cases there was much less fibrin present in the exudation, as compared with cases of pneumococcus, streptococcus, or even acute cases of tubercular meningitis. In the exudation in the meninges of the cord there was less fibrin than in the brain. The fibrin was generally found in masses and not distributed among the cells. In one case it had become converted into large thick hyaline masses. The pus-cells were much more abundant in some cases than in others, and were massed in the meshes of the arachnoid. They were nearly all polynuclear and varied in their distinctness of staining.

Where large amounts of pus-cells were found the nucleus was dim and confused, and could not be sharply separated from the protoplasm. A peculiar feature was the presence of numbers of large cells. These cells varied in size, some of them being as large as the tubercle giant cells. The protoplasm of these cells is finely granular, and contains large vacuoles. A large number of them contained pus-cells which appeared to lie in the vacuoles, and were surrounded by

a clear space. Many of the enclosed pus-cells presented a normal appearance. In others the nucleus was fragmented and the outlines of the cell confused. Most of the enclosed cells were polynuclear leucocytes; occasionally a lymphoid cell was found. In the largest of these cells the cells enclosed were not distinctly outlined, but the large mass contained nuclear detritus and granular fragments evidently derived from broken-down cells. These large cells were generally not found among the pus-cells, but above and below these. Extending out from the sulci where the exudation was most abundant, over the surface of the convolutions, where in some cases nothing but slight dulness could be made out by the naked eye, the meninges were slightly thickened, and this was due almost entirely to the presence of the large cells. Very few pus-cells were found among them here or enclosed in them. The nucleus of these cells is large and vesicular in character. The protoplasm is pale and stains lightly with eosin. The numbers of these cells varied, being most numerous in the oldest cases. They are certainly derived from proliferation of the cells lining the lymph spaces of the arachnoid. Swelling of the cells of the lymph spaces and nuclear figures were made out. In addition to the large cells and polynuclear leucocytes, which made up the chief part of the exudation, there were a few plasma cells, mast cells, and lymphoid cells. In none of these cases examined did emigration appear to be actively taking place at the time of death. The bloodvessels were congested, but only rarely did they contain a greater relative number of leucocytes, and only once were these found in the walls of the vessels. The large cells and lymphoid cells were often found in the adventitia of the vessels. Another feature in the pathological process which distinguishes this form of meningitis from other forms is the absence of proliferation of the intima of the arteries. I have found this present to a greater or less degree in meningitis due to the pneumococcus, the streptococcus, and tubercle bacillus; even in the most acute cases some degree of it may be seen. In none of the cases of diplococcus meningitis was even the slightest degree of it present. The exudation in the meninges in some cases extended into the cortex along the vessels, and there was some slight invasion of the surface of the cortex with polynuclear leucocytes. Slight hemorrhages and collections of pus-cells in both the brain and cord were rarely found.

Organisms were found in the exudation in all cases in which they were demonstrated by culture. In only a few cases were they present in any number. They were found most often within the pus-cells, occasionally free. When free they were in groups, as though set free by the destruction of the cell which contained them. They nearly always preserved the biscuit-shaped diplococcus form, but were occasionally found in tetrads. They stained with Lœffler's methylene-blue and were almost instantly decolorized with the Gram stain. Some of them stained much more brightly than others, and they varied considerably in size. Even in the tissues they stain much less distinctly than do the gonococci. They were only found where the purulent exudation was abundant, and then more generally on the margin of this close to the tissue of the brain and cord. None were found in the thick masses of degenerated pus-cells, nor were they present in the thin exudation extending over the convolutions. Along with these diplococci, which were easily recognized, the cells often contained small, irregular, faintly stained particles, which probably represented degenerated forms. The organisms were found in the tissues both after hardening in alcohol and Zenker's fluid. Beautiful preparations were obtained after hardening in the latter fluid and staining with the polychrome methylene-blue. In the tissues hardened in alcohol they stained better in the Lœffler methylene-blue than in the polychrome.

The lesions found in other organs are secondary. The spleen varies in size, but some degree of hypertrophy was present in all cases. The hypertrophy does not reach the same degree as in most of the infectious diseases. Broncho-pneumonia was found in nearly all cases. In one case the diplococcus was obtained along with other organisms from the foci. The lung lesion could not be regarded as forming a part of the lesions due to the diplococcus, but is probably due to the condition of the patient and to the accumulation and decomposition of products of secretion in the bronchi. In the liver and kidneys parenchymatous degeneration was found. In one case ulceration and abscess of the tonsils was found, from which the diplococci were obtained. In one of Dr. Wright's cases he obtained the organism from the nasal sinuses, although there was no evidence of inflammation beyond slight reddening.

In all these cases cultures were made from the organs, and with

the exception of the cases mentioned, the other organs were sterile. Unlike the pneumococcus the diplococcus intracellularis does not appear ever to produce a general infection of the organism. The organism grown in pure culture shows the following characteristics: It is a micrococcus of about the same size or somewhat smaller than the common pathogenic cocci; it nearly always appears in diplococcus form—two hemispheres separated by an unstained interval. Occasionally single organisms and tetrads appear. In the cultures there is a good deal of irregularity in staining, some organisms being brightly stained, others slightly. Sometimes one of the pair of organisms stains intensely and the other is scarcely stained at all. Usually the two are sharply separated from one another, but in some cases there seems to be a slight amount of material uniting them. Usually the division of the cocci takes place at only one plane; occasionally in two planes, giving rise to tetrads. It has little or no tendency to grow in the streptococcus form, although occasionally short chains of four to six of the organisms are found. In the cultures there is considerable difference in size. The larger organisms stain imperfectly. These variations in size appear to be due to degeneration, and are more conspicuous in older cultures than in the perfectly fresh. It is decolorized completely by Gram's method of staining. The organism grows better on Lœffler's blood-serum mixture than on any other medium. On this it forms round, whitish, shining viscid-looking colonies, slightly convexed, with sharply defined smooth outlines, and may attain a diameter of 1 to 2 mm. after twenty-four hours in the incubator. They tend to become confluent and do not liquefy blood-serum. On agar they form round pearly, translucent, flat, shining, viscid-looking colonies with smooth, sharply defined outlines. Under a low-power they are homogeneous, semi-transparent, and faintly brownish, with transparent sharply defined smooth margins. They readily become confluent. In bouillon the medium becomes only faintly cloudy. At the bottom of the tube is a scanty, grayish-white sediment which rises up as a viscid string when the tube is agitated. On potato it has a feeble growth, and produces an appearance of moisture on the surface. The organism dies out readily. In order to keep cultures going it is necessary to make fresh inoculations every two days. In all cases a large number of the organisms would appear to be dead. This is

seen from the results of cultures of the exudation. When the cocci are present in comparatively large numbers in the exudation smears of this over the surface of the blood-serum do not give rise to lines of growth, but to separate colonies. The same is true in planting. A streak of pure culture blood-serum on agar gives rise not to a growth along the streak, but to separate colonies.

Sugar-agar Stab-cultures. There is no gas production, feeble growth extending along the line of inoculation. In gelatin there is very feeble growth and no liquefaction.

The results of inoculation show that the organism has but feeble pathogenesis. Inoculations were made on mice, guinea-pigs, and rabbits, subcutaneously in the peritoneal cavity, in the pleura and in the spinal canal. The material used was in part pure twenty-four-hour cultures of the organism, in part the fluid containing the organism obtained from lumbar puncture, and in part portions of the meninges. Of a large number of animals inoculated only three guinea-pigs died. Two of these were inoculated in the peritoneal cavity, and one in the pleura. In this case the pleura was injected and roughened with a thin yellowish fibrinous exudation, chiefly at the base, where the injection was most marked. The organism was obtained in pure culture. Cover-slips made from the exudation showed the cocci in large numbers enclosed within the pus-cells. Many of these stained very imperfectly and were apparently degenerated forms. In one of the pigs inoculated in the peritoneal cavity, which died on the second day, there was a sero-purulent peritonitis and little else except some congestion of the lungs. The cultures from the exudate in the peritoneal cavity showed a mixed growth of bacteria, but no colonies of the diplococcus intracellularis. Direct examination of cover-slips showed numerous cocci inside leucocytes, a large number being found in single cells. The third pig, in which 1.3 c.c. were injected into the peritoneum, died twelve hours afterward. The autopsy showed nothing beyond a slight exudation. Microscopically diplococci were found in the pus cells and grew in pure culture. One of the pigs inoculated in the spinal canal showed, after forty-eight hours, slight paralysis of the posterior extremities. The pig was killed, but nothing was found beyond a trauma of the cord at the point of inoculation. Only those inoculations which were made with pure cultures gave any results.

In the preparation of this paper I have been greatly indebted to Drs. Mallory and Leary for their observations at the Boston City Hospital, to Dr. Wright for observations at the Massachusetts General Hospital, and to Dr. Wentworth at the Children's Hospital.

DISCUSSION.

DR. JOHN GUITÉRAS: I have to report two cases of infection by the diplococcus intracellularis, occurring in the hospital of the University of Pennsylvania. The cases are of recent occurrence, and their study is not completed. One of them was a nurse who died with the symptoms of meningitis. The appearances on post-mortem examination were those of a serous meningitis. A microscopic examination has not yet been made. Cultures of the diplococcus were obtained from the fluid.

The other was a case of general infection of a newborn child. There were no local lesions. The diplococcus was found in the blood. A more careful investigation is necessary before I can positively assert that we have to deal here with the diplococcus intracellularis. I do not believe that the existence of the bacteria in the blood excludes the diagnosis of this micro-organism, since I believe that such exceptions are not rare in early life.

DR. F. H. WILLIAMS: In regard to lumbar puncture in these cases, it is chiefly of value in the diagnosis. It does sometimes give relief also, but this is only temporary.

DR GEORGE M. STERNBERG: Have any of the cases got well?

DR. WILLIAMS: Seventy per cent died.

DR. WM. T. COUNCILMAN: There is one point that I intended to mention in regard to the character of the exudation. In some cases the exudation had a marked tendency to extend along the course of the cranial nerves. It was possible to follow it along the optic nerve to the eye, and the auditory and facial nerves were also extensively involved. In some of these cases which have recovered there has been loss of sight and hearing from this extension of the exudation along these two nerves. Eye complications will be found to be due to direct extension of the inflammation from the meninges.

DR. F. C. SHATTUCK: My experience with this epidemic embraces fifteen cases. A peculiar feature in my own experience is that not a child died and not an adult recovered.

ON THE EARLIEST POSSIBLE RECOGNITION OF TUBERCULOSIS.

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At the time of Galen, 160 A.D., and for sixteen centuries after him, phthisis was a suppuration of the lungs, and the disease was recognized by subjective signs, by the expectoration of pus, with fever and emaciation, phthisis ($\phi\theta\acute{\iota}\omega$, I waste), and other gross signs which no one since has described as well as Aretæus, the Cappadocian, who was a contemporary of Galen, and who, like him, had chosen Hippocrates as his model.

Lænnec, 1819, anticipated this stage in the recognition of objective signs, the existence of cavities as established chiefly by pectoriloquy, a coarse symptom about which he associated other finer signs. Louis, 1825, refined these signs so that he could detect the disease at a much earlier period with puerile respiration and prolonged expiration, etc. Piorry, 1840, by percussion appreciated the first deposits, but was not able by this crude exploration to disclose the existence of the disease at any earlier period. Villemin, 1865, opened the door to the pathology of tuberculosis, and actually established the diagnosis by his inoculation of tuberculous matter, but added nothing directly to the earlier appreciation of the disease. Tuberculosis of the lungs continued to be demonstrated clearly only by the physical signs, so that the practitioner had still to rely upon this evidence in making a diagnosis, standing upon the same plane as in the times of Lænnec and Louis. The observations of Villemin, though apparently contradicted by Sanderson, Fox, and other English observers, were confirmed beyond dispute by the experiments of Cohnheim and Salamonsen by the introduction of tuberculous matter into the eye of rabbits. So that it became possible twenty years ago to differentiate absolutely the so-called tuberculous "virus," and the infec-

tiousness of sputum was actually established in a number of experiments made, however, not to determine the nature of the disease of the lungs, but to fix the specificness of matter known to be tuberculous.

The discovery of the tubercle bacillus by Koch, 1882, met with so much opposition that the value of it in the early recognition of the disease was not fully appreciated for nearly ten years. But by the end of that time, 1892, an absolute diagnosis was not accepted without it. So that the recognition of the disease by the presence of the bacillus tuberculosis puts the practitioner on the platform of the beginning of the present decade. Between this and the preceding period there is a lapse of time of fifty years.

Period of Latency. It is now established that tuberculosis pulmonum develops in consequence of the inhalation of the tubercle bacillus from the sputum of other tuberculous individuals. The ignorance of this fact and indifference to it hitherto, with the neglect of the simplest precautions, satisfactorily account for the appalling number of cases of the disease, and account, also, for the insidiousness of the infection. In most cases the source of contamination can be discovered in long and close association with the patient. But the infection may lie latent for years. Childhood is the period of most frequent infection, puberty of most frequent manifestation. Any experience in the diseases of children based upon post-mortem examination shows that the first tuberculous deposits occur in the lungs, to remain perfectly latent, and manifest themselves in signs only after arrival into puberty (Penzoldt.) During this long interval the disease lies latent or shows itself only in general impairment of health, without local sign or with vague local signs—headache, earache, otitis media, nervous dyspepsia, neurasthenia, rheumatoid pains, amenorrhœa, etc. Children who suffer with frequent or more or less continuous malaise, who feel more than others the confinement of the school-room, who are said to be delicate and disposed to phthisis, should be tested for some depot of tuberculosis.

Atmosphere of Infection. Individuals, especially children, who have lived in the atmosphere of tuberculosis, under ignorance of the simple precautions which suffice to protect others, are of necessity infected. In these cases it is simply a matter of degree of infection, so that the history helps toward an early appreciation.

I will mention now a few of the earliest signs:

Odor of Breath. Rosenbach speaks of an odor in the expired air peculiar to phthisical patients. This odor is, he says, like that of bronchitis, but is distinguished by a kind of faint sweetness, due probably to the action of protozoa. I will not dwell upon this symptom, as I have never observed it. D'Estrèe, of Brussels, speaks of an unequal dilatation of the pupils in consequence of irritation of the sympathetic in the cavity of the chest. I have never seen this symptom.

Red Line on Gums. Well known is the red line on the gums, the so-called Fredericq-Thompson line. I attach no importance to it. It is said to be seen most frequently in the young. I have looked for it, but found it only exceptionally.

Clubbed Fingers. Of clubbed fingers I will say nothing, save that they are seen also in certain forms of heart disease. In phthisis they belong to the phthisical habitus, which is interpreted in our day as an already existing infection.

Local Signs. Every obstinate local affection of bones, joints, skin, testis, Fallopian tubes, should excite suspicion. Adenitis is extremely suspicious. Scrofula is tuberculosis and nothing else.

Fever. The importance of anything like a continued or frequently recurring fever, without other known cause, is now universally appreciated. The elevation of temperature may be only a fraction of a degree, but it shows itself every evening and over a period of several weeks or months. This sign has now become so significant as to at once excite the suspicion of tuberculosis. Absolutely reliable conclusions can be drawn only when the temperature will have been taken in the rectum. Observations taken elsewhere are unreliable. I have seen variations as high as 2° F. either way when the temperature was taken in the mouth shortly after cold or hot drinks. The temperature should be taken three times a day. The evening records are most desirable. Anything above 99° F. is suspicious. Malaise and increase of temperature contribute all the more directly to the diagnosis if they are associated with impairment of nutrition, with anorexia, with blood changes, anæmia, especially with chlorosis. I have an oral communication from Klebs, jr., who tests every case without exception with tuberculin, and has never yet failed to get the reaction of tuberculosis in chlorosis.

NIGHT-SWEATS. Night-sweats usually belong to a later period in the history of the disease; in fact, to the septic period; but they sometimes show themselves early, in exceptional cases preceding even cough or any pronounced change in nutrition. I have been able on several occasions to define the cause of night-sweats with great exactness, and in fact to control the condition by the use of test and therapeutic doses of tuberculin.

ALBUMINURIA. Albuminuria is wont to show itself in a slight degree in the earliest stages of phthisis. Tissier speaks of an albuminuria as pre-tubercular, which he notices mostly in the morning, with a concomitant phosphaturia, in a regular intermittent cyclus, preceding all other symptoms of tuberculosis of the lungs. The albuminuria disappeared as soon as the tuberculosis had definitely established itself. I have seen the albuminuria disappear in this way, but I have never seen the phosphaturia in these cases. This albuminuria is not a nephritis. It is a toxic alteration of the albumin, whereby it becomes more dialyzable. Erythesmus cordis, palpitation, and early dyspnœa belong to this same toxæmia.

The appreciation of albuminuria will depend, of course, upon the delicacy of the test. Thus, Spiegler's test, which will detect albumin in the proportion of 1 : 150,000, or, after standing a time, in proportion of 1 : 350,000, discloses it in a large percentage of cases.

Spiegler's test consists of:

℞.—Hydrargyri chloridi corr.	40.0
Acidi tartarici	20.0
Sacchari albi	100.0
Aquæ destillatæ	1000.0

The test must be made with the precaution of adding a drop or two of hydrochloric acid to dissolve the mucin, the presence of which in so many cases of apparent and even real health has led to the erroneous idea of a physiological albuminuria. I have been led up to the detection of a number of cases of tuberculosis by this pre-tubercular albuminuria.

THE DIAZO REACTION. The diazo reaction is in my experience much less common and is less reliable, though it may indicate the tuberculosis which often follows measles. I have no experience with it in this way. The diazo reaction is absent at first, but shows itself suddenly and continuously up to death in the typical miliary

tuberculosis of children. In repeated recurrence it indicates a dangerous process. When it shows this disappearance and reappearance it indicates renewed deposits of tubercles; and when it shows itself in brain affection it indicates that the brain affection is of tuberculous origin.

In miliary tuberculosis the tubercle bacillus may be demonstrated in the blood. Krönig withdraws a few drops of blood, dilutes it with 10 c.cm. acidified distilled water, subjects it to the centrifuge two minutes, and examines the sediment in the usual way for tubercle bacilli. I have had no personal experience with this method. I say nothing of the blood tests proposed specially by Holmes, because I consider them superfluous.

Cough. Cough, which is the commonest symptom of phthisis, sometimes leads us away from chronic bronchitis, chronic pneumonia, and chronic influenza, which may all be independent of tuberculosis. It is the morning and evening cough which is the most suspicious, but any cough which continues for over three weeks should lead to further exploration. We are more apt to be misled in cases in which there is no cough. There may be no cough at all in acute miliary tuberculosis. Latent deposits excite no cough.

The Tubercle Bacillus in the Sputum. The great contribution of modern times came with the discovery of the tubercle bacillus, the presence of which in the sputum establishes the diagnosis, though the absence of it does not exclude it. Much depends upon the source of the specimen, so that the patient must be instructed to bring up matter from the lungs. The fact is he is generally easily conscious of the cough which successfully dislodges a plug of mucus, irritating sometimes to the point of exasperation. Then, again, much depends upon the carefulness of the search. The use of the centrifuge after the fluidification of the sputum by soda or potash shortens the examination and increases the value of the test.

Where failures to find the bacillus seem to be especially disappointing the staining fluids should be tested upon a specimen about which there is no doubt.

The differential diagnosis of tuberculosis includes forms of pseudo-tuberculosis, which occur very rarely in man, but more frequently in animals. The bacilli of pseudo-tuberculosis are disclosed with

the usual aniline coloring, but not by the specific methods used in the study of the tubercle bacillus. These bacilli are distinguished by their capacity of fluidifying the soil by the fact that they decline the Gram coloring, and by their conduct in the inoculation of animals. They have been observed in only one case reported by Cazal and Valliard, as found in caseous nodules in the peritoneum in the autopsy of a man who had previously suffered from dysentery (Pfluegge.)

The lepra bacillus is distinguished especially by inability to inoculate animals with it, and by the lesions characteristic of leprosy at a glance. It must be remembered that leprosy and tuberculosis often coincide. The bacillus found in syphilis is likewise not inoculable in animals. Many color reactions are common with it, but it does not show the same resistance to decolorization with acids. The bacilli found in preputial smegma are very resistant to acids, but not to alcohol, and can, of course, come into consideration in differential diagnosis only in case of secretions obtained from the uro-genital passages.

I say nothing of the search for elastic tissues, which sometimes furnishes valuable corroborative evidence, because by this time there are physical signs.

HEMORRHAGE. Sometimes an hæmoptysis is the first thing. I have known a number of cases to be surprised in the midst of health by hemorrhage from the lungs, which may be even profuse the first time. Sometimes the individual finds the pillow stained with blood, or tastes blood in the morning upon awakening. Under all circumstances the spitting of blood is suspicious, premising, of course, that the blood comes from the lungs. It is not too sweeping an assertion to say that hæmoptysis in apparent health means tuberculosis. If there is any doubt about it, the diagnosis may be established with the assistance of other means.

THE INOCULATION OF THE GUINEA-PIG. A fine test is made by the inoculation of the guinea-pig, the most sensitive of all animals to tuberculosis. The matter is introduced into the peritoneal sac of the guinea-pig, and the peritoneum is examined in the course of two weeks. This test, with the proper precautions, is sure, but is too slow for clinical purposes. It furnishes the best evidence in the clear effusions of pleurisy and pericarditis. But sufficient quantities of fluid must be used to make the test conclusive.

Eichhorst withdrew fluid from every case received in his clinic within the first three days, and injected it into the peritoneum of guinea-pigs. The animals were killed in six to eight weeks, and the internal organs studied for tuberculosis. So long as the experimenter withdrew and injected only one gramme he succeeded in developing tuberculosis only once in eleven cases, and then a tuberculosis of the lymph-glands in the abdomen. When, however, he used a syringe which contained nearly 13 c.cm. he was successful fifteen times in twenty-three cases. Thus he was able in twenty-three cases of serous pleurisy, taken from persons otherwise in the best of health and without a demonstrable disease, showing the lesions of tuberculosis in no other organ, to prove with unassailable evidence that tuberculosis could be produced in fifteen animals—*i.e.*, in 62 per cent. of cases—and that in only eight animals, 34.8 per cent., was tuberculosis absent. It is now known that these numbers are rather too small than too large, so that it may be said that nearly two-thirds of all cases of serous pleurisy are of tuberculous nature.

Aschoff confirms these conclusions. This observer introduced 3 c.cm. pleuritic fluid from fifty-seven cases into the peritoneal sac of guinea-pigs and studied them for tubercle bacilli. The inoculation of guinea-pigs with fluid from twelve cases of the so-called idiopathic pleurisy—that is, such as showed no etiology—produced tuberculosis nine times. The tuberculosis was established in these cases by the microscope, which showed characteristic abdominal lesion.

Pleurisy, therefore, is to be looked upon as a prodrome, and patients have to be warned of the possibility, or, if untreated, of the probability of subsequent developments. The same thing may be said also of similar affections of other serous membranes.

The evidence on the part of pericarditis is not so exact. I have myself had two cases in which fluid compressing the heart was withdrawn by aspiration from individuals of families, other members of which were affected with tuberculosis pulmonum. The relation of tuberculosis to peritonitis and meningitis is well established.

So, too, the inoculation of guinea-pigs with suspected milk, urine, fluids which may contain no or but very few bacilli, may disclose the existence of the disease.

The facts that influenza awakens a latent tuberculosis, and that the disease may attack a patient with well-marked tuberculosis, furnish no justification for the frequent confusion of the two affections, when the differential diagnosis may be, as a rule, so easily established by the examination of the sputum. Chronic malaria has, in common with tuberculosis, fever, sweats, cachexia, and enlargement of the spleen. It is easier to recognize tuberculosis by the proper tests than to discover chronic malaria by examination of the blood.

The dubious cases of typhoid fever are now pretty readily cleared up by the Widal test.

TUBERCULIN. We come now to tuberculin. Koch announced at the Tenth International Congress, at Berlin, 1890, in the discovery of tuberculin an agent which, introduced in proper quantity, would in all cases disclose the existence of tuberculosis. Thus, the injection of one centigramme (one interspace of a 1 per cent. solution)—a quantity which has little or no effect on the individual in health—will produce in the tuberculous a peculiar reaction, marked by chill, with fever, malaise, lassitude, rheumatic pains, sometimes nausea and vomiting, and sometimes an eruption like measles. Visible deposits of the disease—lupus, laryngeal affection, lymph-glands, joint-disease—become hyperæmic, swollen and painful, and in any local infiltrations in the lungs râles are manifested or intensified. These various symptoms, which constitute what is known as the reaction, disappear in the course of four to six or eight hours. Sometimes the reaction is anticipated, sometimes postponed; sometimes it is slight, sometimes severe. But it is manifest in all cases under careful observations with the thermometer. In this way concealed depots of the disease have been revealed, and tuberculosis has been discovered in individuals considered healthy hitherto. The value of this method in the discovery of the disease in man was never rightly recognized, for reasons that will be mentioned later, but in cattle it soon met its proper appreciation, and is perhaps nowhere more extensively and satisfactorily used than in our own country.

I cite one striking observation from abroad. Nocard injected tuberculin into two cows. One of them was thought by everybody, in appearance and symptoms, to be tuberculous; but no reaction occurred. The section showed numerous hydatid cysts in the lungs

and liver, but no tuberculosis. The other cow seemed to be perfectly healthy and strong, but showed reaction. The section showed miliary tubercles in the lungs and intestine.

Observations should be taken in man exactly as in cattle, and in experiments upon cattle with tuberculin Feser found that the temperature should be taken for at least twenty-four hours to get the right picture of the reaction. In one case the temperature increased six hours after the injection, and the rise had entirely disappeared in four hours later. This reaction was considered dubious. The autopsy was made two days after injection. The examination was as thorough as possible. In the animals which did not react every lymph-gland that could be discovered was examined. The animals were found entirely free from tuberculosis, while every animal which distinctly reacted showed tuberculous depots. In three of these cases the depots were so small and concealed that they would have been overlooked under the ordinary examination.

The report of Salmon (United States Agricultural Bureau, *Bulletin* 13, September 19, 1896) concludes with the statement that "thus far we have yet to meet the first case which reacted and did not show tuberculosis upon post-mortem examination."

The use of tuberculin in establishing the diagnosis in man soon met with the objection that a reaction may set in in the absence of tuberculosis. How is it possible to know of these cases that the individual is free from all infection? In fact, we know now that these are cases of complicating or concealed tuberculosis. I have had neither time nor inclination to follow up all the reports of reactions said to have occurred in other diseases—syphilis, lupus, actinomycosis. Of this last disease it was declared, indeed, that the continued use of tuberculin cured it (Eiselsberg). But according to the report of Friedreich, of Leipsic, the so-called febrile actions observed after the injection of tuberculin in actinomycosis could not be referred to the actinomycosis in the cases reported, because the autopsy showed in the lungs abundant tuberculous depots. So, too, in cases of reaction in leprosy it has been found that leprosy and tuberculosis coincide (Pfluegge).

Another objection urged by Klemperer is to the effect that the diagnostic importance of minimal doses (5 mg.) has been rendered illusory from a practical standpoint by the fact that every

human being will show fever who has tubercle bacilli in him, even though they are latent and encapsulated, as in the lymph and bronchial glands. Klemperer claims that "we have no right, from a medical standpoint, to diagnosticate tuberculosis simply on account of the presence of tubercle bacilli in the interior of the body, as only those cases are dangerous which show symptoms and liberate tubercle bacilli with the sputum or other excreta." This objection, which is based upon the theory that ignorance is bliss, falls to the ground in the face of the fact that concealed tuberculosis is a continuous menace, which can, especially at this period, be entirely removed.

A more serious objection was that the reaction sometimes failed when tuberculosis was undoubtedly present. This objection is true, but it applies only for insufficient tests. The observations of Johne, Nocard, Benz, and Jensen show that deeply concealed depots sometimes require repeated and larger doses.

The first test dose for the cases of lightest infection (suspected) should be 5 mg., the second 10 mg., or one centigramme, the third two centigrammes. These doses may be given on succeeding days, or, better, every other day, preferably in the evening, that the temperature records may be properly observed on the following day. Failure to get reaction from these three tests excludes concealed tuberculosis.

It is no practical objection that, as in the case of mallein with glanders, the reaction sometimes fails in very advanced stages of the disease.

The most serious objection, and that which, we might say, killed the general use of tuberculin at the start, was that urged first by Virchow, that tuberculin awakened tuberculosis from latent sources and disseminated the disease. This statement was eagerly caught up and echoed on all sides. Baumgarten believed that under the influence of tuberculin a more rapid and abundant colonization of bacilli occurred in the lungs. Fürbringer went so far as to declare that miliary tuberculosis was found oftener in cases treated by tuberculin than in the non-injected. This authority invoked the aid of statistics in the statement that miliary tuberculosis was found under the use of tuberculin in the lungs in 43 per cent. against 6 per cent. in the non-injected, and a general tuberculosis was found under the use of tuberculin in 21 per cent. against 10 per cent. of the non-injected. These statements, too, were quoted on all sides.

For, to one strong voice there are many echoes. And that is not the worse of it—"there are so many echoes of echoes." I will cite but one of these. A very recent writer in the *Medical News*, in an otherwise good article "On the Modern Aspect of Tuberculosis," abundantly fortified with quotations, says, "the administration of tuberculin in the human subject for diagnostic purposes has been shown to be unjustifiably dangerous, and has been abandoned." This statement, however, was not fortified with quotations, though it might have been. Further, "it is, however, as true to-day as it was before Koch's discovery that we are in no position, at any period before the evidences with which we are familiar can be made out, to say that our patient has or has not tuberculosis."

Now we know of these cases that the observers were confounding the *post* and *propter hoc*, a mistake which is not new in medicine.

It was in vain that the advocates of tuberculin, especially Guttman and Ehrlich, or that those who wished to give it further trial, protested that these results were observed only when the agent was used in too large doses or in too advanced stages of the disease. The popular reaction had set in, so that it had become actually dangerous for a physician to openly acknowledge the use of the agent either as a means of diagnosis or treatment. Medical men followed as hunters do the hounds until the opposition reached such a pitch that a physician sued for malpractice on account of the use of tuberculin could not have found sufficient support in the profession to protect him against an adverse verdict by a more ignorant but not less prejudiced jury. These things are matters now merely of historic interest. Nevertheless, there were individuals in this country, sometimes stigmatized as enthusiasts by men of hastier conclusion, as well as in Europe, who were convinced of the value of the remedy and who continued to use it without regard to the popular clamor. I may mention here Trudeau, Dennison, and Klebs (who employed a modified form), who used it continuously and who made from time to time reports as to the value of the agent.

The danger of dissemination is a spectre which vanishes in the light. The men most familiar with the use of it are emphatic on this point as well as upon the exquisite diagnostic value of it. Thus, Penzoldt, "but I can say positively from my experience that a dose of 0.001 (one mg.) on the first day, followed by a dose of

0.002 on the third day, and 0.003 on the fifth day, doses which are all without injury to the patient, constitutes a most important diagnostic means even under the impossibility of recognizing the disease in any other way."

Wassermann, in speaking of the importance of making a diagnosis in cases of infiltration of the apex from physical signs alone, says, but "in cases in which there is no expectoration the diagnosis may be made only by the injection of tuberculin, which gives an absolutely certain result if it be used in the right way." Springthrope, of Melbourne, a careful and competent observer, confirms this view. He had always found tuberculin safe and reliable when used with discretion, and subsequent experience with the lapse of years confirms his belief in the soundness of his position. Prior says, in summing up his observations on the action of tuberculin: "The use of tuberculin is by no means universal in practice, and the voices against it are loud and numerous. I have myself made use of tuberculin in many cases, and can only say that after the use of it for years, beginning with minimal doses, I have seen no injury, but have often observed surprisingly good results. One must not expect, however, to cure a case of tuberculosis with tuberculin in a few weeks." Klein, working under Weichselbaum, found in his experiments upon animals that minute doses of tuberculin were absolutely unattended with any bad effects.

Moreover, big doses, the biggest possible doses, may be finally given with impunity. Thus, it was observed in the studies with actinomycosis that under gradual tolerance tuberculin could be injected up to the dose of one gramme—that is, a whole bottle at once, as it is sometimes sold—without any disturbance of the general health worthy of mention.

I have myself used tuberculin every day in hospital and private practice for six years in now nearly 1000 cases, and have never seen any kind of evil result beyond the temporary reaction described. Most of my use of the agent has been, of course, in the small therapeutic dose; but in the larger quantity necessary to secure the test reaction I have come to consider it as the best possible, and as a perfectly safe means of diagnosis. But I have had to face so much opposition, and as I think prejudice, as to be delighted to find support in the recent statement of Koch himself.

Koch, April 1, 1897, declares that the fear that in consequence of the reaction the tubercle bacilli would be rendered mobile, and would be thus transmitted to healthy animals, has been shown, in many thousands of tuberculin injections made upon cattle, to be perfectly groundless. "My own individual experience in the use of tuberculin in the early diagnosis of tuberculosis in man in more than 1000 cases coincides with and supports this view. Stabsarzt Dr. Nietner will report in detail upon these cases. In all these cases there was never the slightest intimation of anything like a mobilization or transmission of tubercle bacilli. This experience should entirely annul the foolish prejudice which exists regarding the making mobile of tubercle bacilli, and it should put the diagnostic value of tuberculin in the recognition of tuberculosis in man upon the same plane as in animals."

The following cases of positive and negative evidence, selected from a large number of cases, illustrate the value of tuberculin as a means of diagnosis. I condense the histories to salient points:

Neurasthenia.

Positive evidence. Miss M., aged eighteen years, a tall, fragile, delicate-looking girl, complains of languor, palpitation upon exercise, and easy fatigue. The menses are sometimes delayed. No other anomaly is to be observed. There is no cough and no fever. I had treated the mother of this girl for incipient tuberculosis, the diagnosis having been established by the discovery of the tubercle bacillus in the sputum in the absence of physical signs, and felt sure that the patient had some local depot in consequence of having lived so long in the atmosphere of infection. A test-dose of tuberculin, one milligramme, was given at 2 P.M. Reaction set in on the following morning at 8 o'clock, with chill, fever, temperature of 103° in the course of the day, pain in the bones, headache, etc., the symptoms all subsiding the same night.

Negative evidence. Miss H., aged twenty-two years. Tuberculosis on both sides in the ancestry. Patient very tall, exceedingly slender, emaciated, extremely elongated, cylinder-shaped thorax. Confined to bed for several months. No cough; no fever; good appetite. Test-injections of tuberculin, 0 005, 0.01, and 0.02, negative. This patient is improving rapidly under a pneumatic and general tonic treatment.

Night-sweats.

Positive evidence. J. M., aged twenty-eight years, has had slight cough, morning and evening, for several months, with night-sweats every night. No

other sign of illness. The examination in every way negative. No cough, no bacilli in what sputum he can raise. Fine reaction to tuberculin, the use of which twice a week, in gradually increasing dose, completely arrested the night-sweats in three weeks. Early night-sweats seem to result from the action of toxins, which tuberculin neutralizes.

Sister of Charity, aged twenty-six years. Was brought to the hospital to be treated for night-sweats, with which she had been affected for over a month and which proved refractory to atropin, agaricin, and quinine, but ceased entirely in three weeks under the use of gradually increasing doses of tuberculin.

But that tuberculosis is not the cause of all cases is illustrated in the following report.

Negative evidence. Mr. A. M., aged twenty-two years. Melancholia; sexual neurasthenia; prostatorrhœa; night-sweats for several weeks, occasionally profuse. Test-injections of tuberculin, one, two, and three interspaces (0.001, 0.005, 0.01), negative. The night-sweats ceased and the patient improved in every way under quinine and aromatic sulphuric acid, together with urethral injections of the lactate of silver, 2 per cent., with the Ultzmann catheter.

Joint Disease.

Positive evidence. Mrs. W. C. S., aged twenty-nine years, tall, delicate, pallid. Lived in the house several months with an uncle who died of tuberculosis. Has had one miscarriage one year ago at two months. Complains of general weakness and pains in the trunk, especially on turning. There is some stiffness of the right wrist. No cough, but gets short-breathed on exercise. Temperature 99°. No physical signs save perhaps a slightly defective expansion in the right lung. Test-injection of tuberculin increased the temperature two degrees.

This patient subsequently developed tuberculosis of the right carpus, which finally necessitated the amputation of the forearm. Notwithstanding this extreme measure the patient succumbed to acute tuberculosis three months later.

Negative evidence. Miss F., aged thirty years; Good Samaritan Hospital. Entered March 18, 1897, with a diagnosis of chronic rheumatism. Right elbow swollen; hand and arm cold, blue, anæsthetic. The disease proving refractory to salicylates, iodin and external applications, test-injections of tuberculin, made, one April 17 and one April 19, 1897, 0.01 and 0.02, respectively, gave no reaction.

Tuberculosis Pulmonum.

Positive evidence. W. V., aged thirty-eight years, four children, two tuberculous. Had "lung disease" as a child seven or eight years old, and pneumonia three years ago. Gained weight since from 180 to 150 pounds. Looks like a beer drinker, flushed and flabby. (Says he takes but one or two glasses

a day, but did take up to six months ago half a dozen glasses.) Cough for seven or eight months, with considerable catarrh. Expectorates tough, white mucus. Physical examination entirely negative. Lungs clear, with good expansion.

Examination of sputum shows one or two bacilli, not absolutely clear. Injection of tuberculin, 0.01, at noon produces elevation of temperature 1½° the next morning.

Negative evidence. A physician brought to me his daughter, a young woman, aged sixteen years, with a diagnosis of Bright's disease, because she had had for three months headache, lassitude, and slight albuminuria. The temperature was for the most part subnormal, but showed occasional elevations of ½° to 1°. There was nothing else in the condition of the urine to indicate Bright's disease. The specific gravity was normal. There were no casts. The diazo-reaction was constant. I felt sure that the albuminuria depended upon a change in the albumin from a toxæmia. Although there was no cough, I suspected a latent tuberculosis; but after a thorough test with tuberculin I had to abandon this suspicion. I then tested the blood with a typhoid culture, and found the typical agglutination and arrest of motion of bacilli described by Widal. Having fortified this observation on two subsequent occasions, at intervals of a week, I felt justified in attributing the condition to typhoid fever.

Abdominal Tuberculosis.

Positive evidence. Mrs. A. P., pain and swelling of the abdomen for three months, with gradually increasing weakness and loss of flesh. Temperature subnormal. No cough. No evidence of disease of the lungs; abdomen somewhat distended, obstipation. Palpation reveals nodulation, as from agglutination of the intestine. Satisfactory reaction to tuberculin. Subsequent laparotomy, with recovery.

Negative evidence. Mrs. P., aged forty years, membranous enteritis. No history of tuberculosis, but has had fistula in ano, which excites the suspicion of tuberculosis. Test-injections of tuberculin, one to five interspaces, all negative. Treated subsequently with europhen suppositories. Condition much improved.

Sore-throat.

Positive evidence. K. T., a young woman, aged twenty years, tuberculosis incipiens; has been treated with tuberculin and sustained by it for two years, the disease having made no advance in that time except when the patient interrupts the treatment for several months. Sore-throat appears occasionally, apparently of catarrhal origin; but upon one occasion, under maximum dosage, a crop of ulcers marked by grayish-white deposit appeared about the larynx, with œdematous infiltration of the interarachnoid mucosa. The treatment was interrupted for one week, after which the dose was resumed in less amount, and under gradual increasing dosage the ulcers disappeared.

C. P., aged twenty years, in perfect health "until he was upon one occasion shaved by a barber and had hairs pulled out of a pimple, which had become sore, by means of hair forceps. The barber dug under the skin with his pincers." In two weeks the glands were affected and the general health began to suffer. The throat became sore. Two months later the patient came to me with the glands swollen under the right jaw, the arm, and in the right groin. In the course of a week sore-throat set in, with uniform redness and swelling and with the formation of one ulcer on the side of the veil of the palate. I suspected first an accidental inoculation of lues, and treated the patient with mercurial inunctions and iodine. There was no material improvement under this treatment. As I had previously treated a member of the family for tuberculosis pulmonum, it occurred to me to make a test injection of tuberculin. This injection was followed by typical reaction. Hereupon I commenced the regular treatment, finding that every increase in the dose was attended by the manifestation of tuberculous deposits in the throat. It appeared as if colonies of bacilli under the mucosa had been brought to the surface by the tuberculin. They were always soon destroyed by local applications of nitrate of silver in stick, and the patient made a good recovery after three months' treatment with tuberculin.

Negative evidence. Miss H. has been aphonic for several weeks. The voice was husky for months. The general health has been poor. There is considerable pallor and apparent weakness, but no fever or sweats. The voice is lost. The patient expresses herself in whispers. There is no cough and no sputum. The examination of the chest is entirely negative. The larynx is catarrhal throughout. The epiglottis is heavy and conceals the interior. At times, however, there may be obtained a glance within the throat, revealing a thickening, rather a reddish, gelatinous looking mass on the middle of the left vocal cord. It is undoubtedly this mass which prevents approximation of the cords and causes the aphonia.

Was the deposit tubercular? I could not tell. A test-injection of one milligramme gave no reaction. A second injection of five milligrammes gave no reaction; a third injection of ten milligrammes—*i. e.*, one centigramme, gave no reaction. Hereupon I excluded tuberculosis, cocainized the throat, touched the gelatinous mass twice with the nitrate of silver melted upon the end of a laryngeal probe. The mass melted away and the patient recovered the use the voice in two weeks.

I could much multiply these reports from my own case-book, but perhaps enough have been cited to establish my position.

The importance of an early diagnosis needs no more mention here than a repetition of a well-known fact that the disease, at all times amenable to arrest at this stage, has now, under the use of the perfected tuberculin, probably become subjected to absolute cure. It is the arrest or cure at this stage which avoids or prevents the mixed infections which give the disease its gravity.

The examination for sputum should include search for the influenza bacillus, for the diplococcus of pneumonia, and for the streptococcus and other pyogenic micro-organisms. The exclusive presence or predominance of these micro-organisms determines the complications of tuberculosis. Most patients, as we now know, succumb, not to tuberculosis, but to sepsis. The failures in the treatment of the disease in man with the specific remedies hitherto employed are largely due to the fact that tuberculosis in man becomes in the later stages a mixed infection. These are the cases which are benefited most by creosote, climatotherapy, etc. Jakowski developed pyogenic bacteria nine times in seven patients from the blood of hectic fever. But, as Hewelke concludes, negative findings in the blood do not justify negation of mixed infection in pulmonary tuberculosis.

These studies will give us new subdivisions and new names—streptomycosis, staphylomycosis, etc.—but in the meantime tend to reinstate the old term, phthisis, by the demonstration that tuberculosis pulmonum is only one of the forms of this disease. This observation does not underrate the gravity of tuberculosis, because it is the tubercle bacillus which prepares the way for the invasion of the secondary or pyogenic micro-organisms. We may now distinguish between the uncomplicated tuberculosis which marks only a small percentage of all cases of lung disease, runs a course without fever, or, if fever exists, is unfavorable because the disease is then so far advanced. These uncomplicated cases are especially suitable for tuberculin treatment. Most cases of later course represent infection with the streptococcus, and these cases are to be separated into those of active course with fever, and passive without fever. The distinction lies chiefly in the fact that in the first case the parenchyma of the lungs is attacked with the streptococci, while in the second the streptococci lie only in superficial colonies in the bronchi, etc. (Spengler.) Rarer cases are mixed infections with the pneumococcus, micrococcus tetragenus, staphylococcus, influenza and pseudo-influenza bacillus. All these forms, associated with fever, are to be treated with tuberculin only tentatively until the complicating affections have been subdued, if they can be, by the open-air treatment, by creosote, cognac, climate, etc. Most of the cases of phthisis are readily recognized as such, and need no test injections, but the diagnosis in our day demands a differentiation of cases.

Moreover, the diagnosis should be declared sooner, for it is plain to see now that the earliest possible appreciation will lead to the extinction of the disease.

DISCUSSION.

DR. F. C. SHATTUCK: A considerable experience for several years with the use of tuberculin for diagnostic purposes has convinced me that it is not harmful. Apart from the disturbances for twenty-four to forty-eight hours, I have never seen ill effects from it. It seems to afford us distinct aid in diagnosis in doubtful cases, and yet it may lead us astray, as shown by the following case: A girl, nineteen years of age, had a mobile epigastric tumor of uneven surface. She reacted typically to tuberculin, and for this and other reasons not necessary here to mention, we thought it more probable that she was the subject of tubercular disease of the abdomen, probably of glandular origin, than of malignant disease of the stomach. An autopsy some months later revealed sarcoma of the pylorus, peritoneum, and other parts, and an old tubercular focus in the apex of the right lung which had given rise to no physical signs. The frequency of tuberculosis, even in a latent form and giving rise to neither rational nor physical signs must be borne in mind and allowed for.

DR. A. LAWRENCE MASON: Tuberculin has been used in the Boston City Hospital for diagnostic purposes for some years, and has never had any bad effect, so far as my experience goes. I believe it will be especially valuable in enabling us to decide upon laparotomy in cases of tubercular peritonitis, when the diagnosis is doubtful.

ON THE BLOOD-PRESSURE-RAISING CONSTITUENT OF THE SUPRARENAL CAPSULE.

By JOHN J. ABEL, M.D.,

AND

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Both clinical experience and laboratory research have shown that the suprarenal capsule is an organ of vital importance. Physiologists[1] have proved that a very small quantity of an aqueous extract of the medullary substance raises the blood-pressure to a great height above the normal. It has also unequalled power in reviving a poisoned heart. Gottlieb,[2] for example, has shown that it will revive the heart of a rabbit which has practically stopped beating in consequence of an intravenous injection of chloral hydrate. Bates[3] applied an aqueous solution to the eye and found that it exerted a marked vaso-constricting action. In numerous cases of congestion a small quantity dropped into the conjunctival sac brought about an immediate pallor, lasting for some time. According to this writer, the extract is very useful in prolonged operations, for, when repeatedly applied, hemorrhage is prevented and cocaine anæsthesia is in consequence indefinitely prolonged. As a result of his two years' use of the extract Bates concludes "that within the limits of its sphere of activity there is absolutely no other substance which can take its place. Other experiments[4] go to show that the

[1] Schäfer and Oliver. Journal of Physiology, xvi. (1894) and xvii. (1895); Szymonowicz and Cybulski, Wiener med. Wochenschrift, 1896, No. 6.

[2] Arch. f. exp. Pathol. u. Pharmakol., xxxviii. p. 106.

[3] New York Medical Journal, 1896, lxiii. p. 647.

[4] Foa and Pellacani Cited in Maly's Jahresb. d. Thier-Chemie, xiii. 129; Marino-Zuco, ibid., xviii. 231; Gourfein, Rev. Méd. de la Suisse Romande, October 20, 1895; Compt. rend. 1895, cxxi. 311-311.

aqueous extract is a powerful poison when injected directly into the circulation, and may lead to fatal results.

The various extracts that have been used in these experiments were mixtures of unknown substances, and it is as yet an unsolved question whether the various actions at present ascribed to the gland are due to one and the same substance.

We are at present interested in the isolation of the blood-pressure-raising constituent, for in a purified state, separated from all other constituents, it might become a therapeutic agent of great importance. On the chemical side but little advance has been made over Vulpian's[1] striking original contribution more than forty years ago. Vulpian observed that the juice expressed from the suprarenal capsule of many different animals behaved in a striking manner toward ferric chloride and toward solutions of iodine, giving with the former reagent an emerald-green color and with the latter a beautiful rose-carmine tint. No other tissue of the body, so far as investigated by Vulpian, gave these reactions. Virchow[2] substantiated Vulpian's statements, but added nothing new. A year after Vulpian's first announcement his second paper appeared in conjunction with Cloëz,[3] verifying and extending his first observations and stating his failure to isolate the chromogenic substance or substances to which the above reactions are due.

Equally unsuccessful were Arnold[4] and Holm.[5] Krukenberg,[6] years after, repeated the work of Arnold and came to the conclusion that the chromogen of the suprarenal capsule is a non-volatile, nitrogenous, and ferruginous organic acid, which is probably related to the turacin of the musophagidæ and to chlorophyll. He assumed that the substance giving the green color with ferric chloride is not the chromogenic substance of Vulpian, but more likely pyrocatechin accompanying the chromogen. Attention being thus attracted to the possible occurrence of pyrocatechin in the suprarenal capsule, others took up the subject.

Brunner[7] found that an alcoholic extract can be made to give

[1] Note sur quelques reactions propres à la substance des capsules surrénales, Compt. rend., 1856, xliii, 665-663.

[2] Virchow's Archiv, 1857, xii, 481-488.

[3] Compt. rend., 1857, xlv. 340-343.

[4] Virchow's Archiv, 1866, xxxv, 64-107.

[5] Journ. f. prakt. Chemie, 1867, c. 150.

[6] Virchow's Archiv, 1885, ci. 342-391.

[7] Schweizer Wochenschr. f. Pharmacie, 1892, xxx. 121-123.

nearly all of the reactions of pyrocatechin; thus it gives the well-known green color with ferric chloride, passing into a fine red on the addition of ammonium tartrate and a few drops of an alkali; it reduces silver nitrate at room temperature, and Fehling's solution on boiling. The addition of an alkali soon causes it to take on a dark brown color; lead acetate gives a precipitate, sodium nitroprusside and very dilute ammonia give a wine-red color. All of the above reactions being given also by pyrocatechin, Brunner concluded that Krukenberg was right in his belief that pyrocatechin is present in the suprarenal gland.

After the discovery of the blood-pressure-raising property of the suprarenal gland, B. Moore,[1] working in Schäfer's laboratory, came to the conclusion that Vulpian's chromogen and the blood-pressure-raising constituent are identical. He based his opinion on the fact that chemical operations which destroy the color reactions by oxidizing the reducing agent appear also to destroy the blood-pressure-raising constituent. That the solubilities of the active principle are the same as those of the reducing agent appears also to support this opinion.

Frænkel[2] worked with residues obtained with the help of alcohol and acetone as solvents. These residues raise the blood-pressure and do not contain pyrocatechin, and on the strength of the ferric chloride reaction and its reducing power he concludes that the essential principle of the residue is a nitrogenous derivative of the *ortho*-dihydroxybenzene series.

According to Frænkel, both Krukenberg and Brunner are wrong in their opinion that the suprarenal gland contains pyrocatechin. Frænkel concludes, like Moore, that the blood-pressure-raising constituent and Vulpian's chromogen are one and the same substance.

More recently still, Mühlmann[3] has attempted to prove that the blood-pressure-raising constituent is a pyrocatechin derivative. He asserts that on boiling fresh suprarenal capsules with dilute hydrochloric acid the active principle is decomposed and the pyrocatechin which is split off may be taken up with ether. Mühlmann has not, however, furnished conclusive chemical proofs for his assertion.

[1] Journal of Physiology, 1895, xvii. Proc. Physiol. Soc., p. xiv.
[2] Wiener med. Blätter, 1896, No. 14–16.
[3] Deutsche med. Wochenschr., 1896, No. 26, 409–411.

Both Mühlmann and Brunner might have settled this point by precipitating the supposed pyrocatechin with lead acetate and analyzing the lead salt thus obtained. Pyrocatechin may be present in small amounts in the gland, but no proof of this has yet been furnished.

There is, therefore, at present great diversity of opinion as to the chemical character of the blood-pressure-raising constituent of the gland. Whatever the probability may be of the correctness of this or that view, it is to be noted that all of the above-named investigators have based their conclusions on reactions made with aqueous, alcoholic, or acetonic extracts; none of them have even roughly isolated a definite chemical compound. The subject is one of great difficulty, and our own work is at present merely preliminary, but we have arrived at the following conclusions, which we believe to be borne out by our experiments:

First. We have found by isolating the blood-pressure-raising constituent in the form of a benzoyl compound and decomposing it that the active principle is a substance with basic characteristics, and that it must in all probability be classed with the pyrrol compounds or with the pyridine bases or alkaloids.

Second. That pyrocatechin cannot be split off from the isolated active compound by boiling with acids, as has been asserted.

Third. We have found that a carmine-red pigment can be separated from the sulphate of the active principle without destroying its power to raise the blood-pressure.

Fourth. In addition to this, we have isolated from the crude benzoyl product a volatile basic body which fumes in the air and which emits an odor very much like that of coniine.

Method of Isolating the Active Principle in the Form of a Benzoyl Compound.

We have used sheep's glands in large quantity. The medullary substance of the fresh glands was scraped out, dried on the water-bath at 60° C., ground up finely, and extracted with ether for several days until the fats and the substance known as Manasse's jecorin were removed. In this way a fine dry powder of a grayish-white appearance is obtained, the aqueous extract of which is very active in raising the blood-pressure.

With 100 grammes or more of this powder, representing one kg. in weight, or about 1000 fresh glands, we proceeded as follows: The powder was repeatedly extracted with warm water acidulated with a few drops of dilute sulphuric acid until the gland had yielded up all of its chromogenic substances, as tested by Vulpian's reactions. This aqueous extract was evaporated on the water-bath to a small bulk, a large excess of strong alcohol was then added, and the whole allowed to stand twenty-four hours, by which time the proteids had all settled out. The alcoholic fluid was then filtered and the greater part of the alcohol removed by distillation; the remainder was driven off on the water-bath. The entire removal of the alcohol is necessary, and in order to avoid too great concentration of the acid fluid, which seems to destroy some of the active principle, water has now and then to be added. The brownish fluid when filtered gives all the well-known reactions characteristic of Vulpian's chromogen, and on neutralizing the sulphuric acid we found the filtrate to be physiologically very active.

This filtered fluid is next treated with the proper quantity of benzoyl chloride and sodium hydrate, according to the Baumann-Schotten method of forming a benzoyl compound. There results a tarry substance of a light yellow color, which sticks to the sides of the separator funnel, and which is collected and washed until the wash fluid no longer gives an alkaline reaction. It is next dissolved as far as possible in alcohol and the alcohol evaporated. The residue is then treated with ether, which takes up the greater part of it, the ethereal solution is filtered and the ether driven off.

The residue, which is of tarry consistence and amber color, is taken up in strong alcohol from which all basic substances have been removed by distilling from tartaric acid. It is then boiled for two hours with animal charcoal previously well washed with purified alcohol. After filtration and the evaporation of the alcohol a considerable quantity of crystalline residue is obtained, which is found to consist of the benzoyl compound of the active principle contaminated with other benzoyl derivatives, and which we may call the crude benzoyl product. It is insoluble in water, alkalies, or acids of ordinary strength; is soluble in alcohol, ether, glacial acetic acid, and concentrated sulphuric acid.

It is of interest in this connection to note that benzoyl chloride

effects the complete removal of the blood-pressure-raising constituent from an aqueous solution. This is proved by the fact that the filtrate from the insoluble benzoate no longer gives the characteristic chemical reactions of the active principle, and that chemical manipulations no longer yield a blood-pressure-raising constituent. Indeed, an injection of a sufficient amount of the material left after the sodium benzoate and the excess of alkali have been removed causes a sharp and sudden fall of pressure, instead of a rise.

It was not until long after we had made use of benzoyl chloride as a precipitant of the active principle that we obtained access to Frænkel's[1] paper. From it we learned that a syrupy substance is thrown out when benzoyl chloride is shaken up with a pyridine solution of an extract of the gland. Frænkel did not succeed in crystallizing this benzoyl compound, nor did he attempt to decompose it in order to ascertain whether it was in reality a benzoate of the blood-pressure-raising principle.

Methods of Decomposing the Benzoyl Compound.

A quick method always used by us as a qualitative test is as follows: The compound is dissolved in as little concentrated sulphuric acid as possible, crushed ice is slowly added, and the benzoic acid which has been split off is shaken out with ether. On neutralizing the solution we found it to give the reactions characteristic of aqueous solutions of the medullary substance. We have not considered this method adapted to the decomposition of large quantities of the product.

Decomposition of this benzoyl product was effected by means of an alcoholic solution of sodium alcoholate and also with strong hydrochloric acid and alcohol, but these methods were found to be less satisfactory in practice than the following, which is the method on which we now rely. The benzoyl compound is dissolved in glacial acetic acid, the solution heated to near the boiling-point, and an equal volume of a 25 per cent. solution of sulphuric acid, actively boiling, is slowly poured into the hot acetic-acid solution, the whole being shaken meanwhile. The flask is now attached to a back-flow condenser and heated on a small flame for about ten minutes.

[1] Wien. med. Blätter, 1896, No. 14-16.

The solution is next diluted with water and allowed to cool, the benzoic acid, which has been thrown out, is filtered off, and the rest is removed with the help of ether. Mixed with the benzoic acid which has been removed by filtration is found a dark, brittle substance, which softens on the water-bath, and which we assume to be a benzoyl compound of unknown composition which was apparently unaffected by the dilute sulphuric acid. On dissolving it in concentrated sulphuric acid and diluting with crushed ice, the resulting fluid gives none of the reactions characteristic of suprarenal extracts.

After decomposing the benzoyl product with hot dilute sulphuric acid and removing the benzoic acid thus split off we next get rid of the acetic acid by repeated partial evaporations, taking care not to let the solution become too concentrated, and thus perhaps injure the active principle. After the removal of the acetic acid the sulphuric acid is precipitated with the help of lead carbonate. The lead sulphate is removed and the filtrate is allowed to stand *in vacuo* over sulphuric acid until it has become of tarry consistency. It is then exhausted with ether, acetone, and absolute alcohol in succession. The residue is physiologically very active, and it gives all the reactions characteristic of an aqueous solution of the gland—a beautiful rose color on the addition of an alkali, a green color with ferric chloride, reducing silver nitrate, etc.

However, we are not yet dealing with a pure substance. If we neutralize an aqueous solution of the product thus obtained with a free alkali or with a carbonate of the alkalies, an overpowering odor, much like that of coniine, is perceived. As this odor passes that of pyridine seems to take its place. The basic substance thus liberated fumes in the air or when a glass rod moistened with hydrochloric acid is brought into its neighborhood. To remove this basic substance we made an aqueous solution of the active principle as above isolated, rendered it faintly alkaline with sodium carbonate, and shook out with ether several times in succession. But this method did not remove all of the coniine-like substance. To effect this we were obliged to make the active principle strongly alkaline with sodium hydrate before shaking out with ether. The aqueous solution, in consequence of the addition of the free alkali, takes on a deep red color, and carmine-red flocks are thrown out. After the removal of the coniine-like substance with ether the fluid containing

the red flocks was acidulated with sulphuric acid and the carmine-red substance was filtered off. The clear filtrate, which was a pale straw color, was concentrated *in vacuo* and the active principle taken up in weak alcohol. On account of the insolubility of the sulphate of the active principle in absolute alcohol it is difficult to obtain this entirely free from sodium sulphate. We hope in future to remove both the coniine-like substance and the pigment with the help of ammonia. The presence of pyridine in our ammonia prevented our using it for this purpose.

This volatile base of a coniine-like odor has not hitherto been described as a constituent of the suprarenal capsule. The beautiful carmine-red pigment we take to be identical with the red substance which many other observers have found to be thrown out as a precipitate when ammonia is added to a concentrated aqueous solution of the gland or when a solution is evaporated in the presence of lead acetate.[1] Others have believed this red precipitate to be the oxidation-product of the active principle of the gland, but we shall presently see that the active principle is still present in the filtrate from the carmine-red body. We have as yet made no experiments with this pigment except to note that it is but slightly soluble in dilute alkalies and insoluble in dilute acids, and that iodine destroys the color. Our method appears to make the further study of this substance possible.

The coniine-like substance we have secured in the form of its hydrochlorate, and with it we have made certain studies which will be published at a later date.

Characteristics of the Blood-pressure-raising Constituent as obtained by Decomposing its Benzoyl Compound.

We have now obtained the active principle in the form of a sulphate. As thus far isolated it is a hygroscopic, straw-colored residue which tends to crystallize on standing over sulphuric acid, agglomerates of small crystals forming on the edge of the bowl and the entire residue taking on a semi-crystalline appearance. The sulphate does not contain the volatile, coniine-like substance, nor do we find the

[1] Holm, Journ. f. prakt. Chemie, c. (1867) 150.

carmine-red pigment which falls out on the addition of an alkali. Alkalies no longer liberate the coniine-like substance, nor do they throw out the red pigment, but they cause a brownish discoloration, and, on heating, alkaline vapors, probably ammonia, are given off.

Our sulphate is very active physiologically. A small quantity suffices to raise the blood-pressure, as seen in Fig. 1 (page 477), and it is therefore evident that we have isolated the active principle, but slightly contaminated with other substances.

A final product even more active in small quantities is that whose action is shown in Fig. 2 (page 478), where the mercury is driven out of the manometer. This more active compound still contains much of the coniine-like substance, and at once throws out the carmine-red pigment on the addition of alkalies. The sulphate of the coniine-like substance does not, as we have seen, raise the blood-pressure; it therefore remains for us to consider whether the carmine-red substance which is precipitated on the addition of alkalies, either alone or in conjunction with small quantities of oxidizing agents, has any physiological significance or stands in any chemical relation to the blood-pressure-raising constituent. We incline to the opinion that this substance, which in the original aqueous solution of the gland gives with iodine water the "teinte rose-carmin tout à fait remarquable" of Vulpian, is in nowise connected with the blood-pressure-raising constituent. We have repeatedly removed or destroyed this substance by boiling solutions containing it with strong ammonia or with sodium hydrate, and have always been able to separate subsequently an active material. In proof of this we append Fig. 3 (page 479), showing a great rise of blood-pressure, although the material from which this active principle was obtained had been boiled for an hour with a 5 per cent. solution of sodium hydrate. After such treatment with alkalies care must be taken in the subsequent evaporation of the alcohol with which the active principle is removed to keep an acid reaction, as otherwise the greater part, if not all of it, will be destroyed by oxidation; and unless all evaporations are carried on under reduced pressure, much material will be lost, even with the above precaution.

Although somewhat contaminated with its own decomposition-products, this final sulphate has all the characteristics of an active substance. As shown by repeated experiments, it promptly raises

the blood-pressure, it constricts the vessels of an inflamed eye, and when injected into the dorsal lymph-sac of the frog it acts like a narcotic or cerebro-spinal poison.

As freed from the red substance the sulphate of the active principle behaves as follows: It is very soluble in water, fairly soluble in weak alcohol (50 per cent.), almost insoluble in absolute alcohol, and quite insoluble in ether, acetone, ligroine, and chloroform. Its aqueous solution, even when freed from adherent sulphuric acid, has a slightly acid reaction. The addition of iodine water to a neutral solution does not give a rose-red color. Alkalies added to a strong solution give a brown color, which deepens on heating. Ferric chloride gives a purplish brown, almost black in concentrated solution, which, on the addition of tartaric acid and an alkali, passes into a deep red color. Before the removal of the carmine-red substance the addition of ferric chloride gives the well-known emerald-green color, which passes into red on the addition of an alkali.

It is evident that our sulphate gives Vulpian's ferric chloride reaction, though somewhat changed by the removal of what we take to be the chromogenic substance which gave his iodine reaction. It also promptly reduces silver nitrate in alkaline solution, but does not reduce Fehling's solution even on boiling.

Probable Relation to the Alkaloids.

More than a year ago, during our first studies with suprarenal extract, we were struck with the fact that every extract entirely free from proteids and physiologically active gave a fine pyrrol reaction when subjected to dry distillation. This is evidenced both by the odor and by the pine-sliver reaction. A small quantity of the isolated sulphate also gives the pyrrol reaction when heated either alone or with zinc dust.

We attach considerable importance to this reaction. As is well known, alkaloids in general give pyrrol on dry distillation; morphine, for instance, on being heated with 10 parts of zinc dust gives off pyrrol, ammonia, trimethylamine, pyridine, phenanthrene, etc.[1]

[1] We are well aware that certain salts of glutaminic, pyromucic, and its allied acids also yield pyrrol on dry distillation. These compounds, however, like the proteids and their allies, appear to us to be excluded.

During the past winter we made several attempts to prove the presence of pyridine among the products of dry distillation of the active principle as above isolated, as its detection would prove that our principle was to be classed among the alkaloids.

In attempting to show the presence of pyridine we heated the active principle with zinc dust in a current of dry hydrogen and passed the distillation-products through a test-tube and two small flasks, the tube being placed in a cooling mixture, the first flask being partly filled with dilute sodium hydrate and the second with dilute hydrochloric acid.

At the close of the experiment the test-tube gave off alkaline vapors that smelled strongly of trimethylamine and had in addition a peculiar, sweetish odor. The contents of the test-tube diluted with water gave a precipitate with bromine water and with copper sulphate, but with the latter reagent the fine blue color characteristic of pyridine did not appear. The presence of amines seems to render difficult the detection of small quantities of pyridine. The contents of the third flask, on exposure to the air, took on a rose-red color, and after a time threw out a precipitate of the same tint. Both flasks gave off the odor of benzaldehyde.

The following experiment was also made with a little of the sulphate, which no longer gave the red-rose reaction with iodine, but which still contained a little of the coniine-like substance. For two hours it was kept at 150° C. in a sealed tube with 25 per cent. hydrochloric acid. On shaking out with ether a considerable crystalline residue was obtained, which, without much purification, melted sharply at 120° C. and had all the properties of benzoic acid.

In the above decomposition-experiments the quantity of material at command was small, perhaps not more than one-fifth of a gramme at a time, and not entirely pure. We do not, therefore, lay much stress on our failure to detect pyridine.

The fact that the nitrogen of our compound is given off in the form of amines and pyrrol gives strong ground to believe that our substance is to be classed with the pyridine bases, using this term in a broad way. Its basic character, its ability to take up acid radicles, as illustrated by the formation of a benzoyl product; its reducing power, and its color reaction with ferric chloride, are all points which can be urged in support of this view. Furthermore, cupric

acetate, the serviceableness of which as a precipitant of carbo-pyridine bases has been shown by Gautier and Landi,[1] also precipitates our active principle; and iodine chloride, which Dittmar[2] found to give brown or yellow halogen addition-derivatives with a large number of the alkaloids, gives with a neutral or slightly acid solution of our active sulphate a brownish, flocculent precipitate.

Of less weight in this connection, but nevertheless of some value, is the fact that its physiological action and its power in small doses is again in accord with what is known of alkaloids. Strychnine, thebaine, and other alkaloids are readily called to mind as able to raise the blood-pressure, and recently Tunnicliffe[3] has placed piperidine in the same list. The pyrrol[4] bases are also physiologically active, although less attention has been paid to them.

Pyrocatechin cannot be Split off from the Blood-pressure-raising Constituent.

As already said, Mühlmann has stated with great positiveness that the blood-pressure-raising constituent is pyrocatechin joined to some other substance, probably an acid. Mühlmann does not offer sufficient proof for his conclusion, and even had he proved the presence of pyrocatechin in the gland itself, this is a very different thing from showing that it enters into the chemical constitution of the blood-pressure-raising constituent.

We have repeated Mühlmann's work, and have found that after boiling the medullary substance with hydrochloric acid the ether takes up a trace of Vulpian's substance as well as a substance that reduces Fehling's solution.

The ether residue also gives a precipitate with neutral lead acetate, which, on decomposition with dilute sulphuric acid, sets free a compound that gives with ferric chloride the reaction so characteristic of pyrocatechin. Our blood-pressure-raising constituent is not precipitated by lead acetate, and could not, therefore, have been responsible for this result.

Furthermore, on decomposing a fairly large quantity of the crude

[1] Compt. rend., cxiv. (1892) 1154–1159.
[2] Berichte d. deutsch. chem. Gesellsch., xviii. 1612.
[3] Centralb. f. Physiol., x. No. 25, 777.
[4] Jac. Ginzberg, Ueber das Verhalten des Pyrrols, etc., Inaug. Diss., Königsberg, 1890.

benzoyl product before referred to and shaking out the resulting benzoic acid with ether we have twice found that the ether has taken up, in addition to the benzoic acid, a small quantity of a substance which reduces Fehling's solution and gives a precipitate with neutral lead acetate. On decomposing the resulting lead compound with dilute sulphuric acid and neutralizing the filtrate we obtained a solution which behaved with ferric chloride in the way characteristic of pyrocatechin. The quantity of this lead compound obtained has been too small for analytical purposes.

We consider it, therefore, still uncertain whether or not a little pyrocatechin is present in the gland. That the blood-pressure-raising constituent is, however, not a pyrocatechin derivative seems to us certain. To prove this we used not the entire gland, nor the medullary substance, but the active principle itself, as isolated by us by decomposing the benzoyl compound.

We have used large quantities of material, representing in each experiment the active principle of several thousand glands. We have boiled this with hydrochloric acid of varying strength and for varying lengths of time, and in no case have we been able to find in the ether used as a solvent any trace of a substance that would reduce Fehling's solution or give a precipitate with lead acetate. Inasmuch as some of the chromogenic substance always passes into the ether from acid solutions, these two reactions are both necessary to establish the presence of pyrocatechin. In other words, we have failed to split off pyrocatechin from the active principle as isolated by us. If present, it could hardly have eluded our search, for even a minute quantity may be made to give a precipitate with neutral lead acetate.

We propose during the coming autumn to continue this work. Having made arrangements for the use of a large amount of material, we hope to secure both the benzoate and the sulphate in a form pure enough for analysis and for further chemical study.

Summary.

We may summarize the results of our work as follows:

The blood-pressure-raising constituent of the suprarenal capsule may be completely precipitated from an aqueous extract by treatment with benzoyl chloride and sodium hydrate, according to the Schotten-Baumann method.

On decomposing the resulting benzoyl products a residue is obtained which possesses great physiological activity. It gives the color reactions of Vulpian, reduces silver nitrate, and possesses the other specific qualities of suprarenal extracts.

With the help of alkalies a carmine-red pigment may also be separated from these decomposition-products. We take this pigment to be that one of the chromogenic substances of Vulpian which gives the rose-carmine color when suprarenal extracts are treated with oxidizing agents or alkalies.

A volatile basic substance of a coniine-like odor is always found to accompany the crude benzoate. When these substances are removed the active principle is left as a highly active sulphate or hydrochlorate, as the case may be. It is therefore a basic substance. Its salts give a color reaction with ferric chloride; they also reduce silver nitrate, but not Fehling's solution.

It is not possible to split off pyrocatechin from this isolated active principle. The fact that dry distillation causes the appearance of amines and pyrrol in abundance, taken in connection with its ability to take up acid radicles, its reducing power, its precipitability by cupric acetate and iodine chloride, and its physiological action, lead us to conclude that our active principle is to be classed with the pyridine bases or alkaloids.

Addendum, June 15, 1897.

Since the foregoing paper was read B. Moore has published a paper in the *Journal of Physiology*, vol. xxi., Nos. 4 and 5, May 12, 1897, entitled "On the Chromogen and on the Active Physiological Substance of the Suprarenal Gland." In this paper it is suggested that the active principle may be a pyridine derivative. Moore's conjecture is based, first, on a formula calculated by him from a combustion analysis of Krukenberg, made with an impure, hygroscopic, non-crystalline residue obtained by merely decomposing and drying a precipitate secured out of an alcoholic extract of the gland with the help of basic lead acetate. The calculated formula, the carbon content of which differs by 1.33 per cent. from that actually found by Krukenberg, is $C_5H_{14}NO_4$, and Moore points out that in it the ratio in which the elements carbon and nitrogen stand to

each other is the same as in pyridine, C_5H_5N. Now such a calculation, though suggestive to the investigator, furnishes no proof of the presence of pyridine, for Krukenberg could not possibly have had in hand a chemical individual uncontaminated with other constituents of the gland. Krukenberg himself admits that his material was a mixture of unaltered pigment and its decomposition-products. It is also certain that it was contaminated with other constituents of the gland. This is proved by the fact that basic lead acetate precipitates several of the constituents of the gland which pass into alcohol, and also by the fact that the analyzed material contained 0.068 per cent. of sulphur and from 1.18 per cent. to 1.44 per cent. of ash.

A second reason given by Moore in support of his conjecture is that when "some suprarenal extract was cautiously fused with caustic potash, so as to avoid charring, the peculiar odor of pyridine was at once obtained." He admits that proteids were present in this extract, and that pyridine and its homologues are formed in the destructive distillation of proteids, but states that the experiment was "conducted so as to avoid charring," and considers this a sufficient safeguard. This experiment has also no value, for the odor of pyridine can always be obtained when a mixture of dry, powdered proteid and powdered caustic potash are fused together so as to avoid charring. This experiment, therefore, must be made with material entirely free from proteids. Since reading Moore's paper we have fused a little of our active principle with caustic potash, but have failed to detect pyridine. If present in the molecule of the active principle, it is evident that larger quantities of the material must be used to prove it. Only indisputable chemical proofs can establish the presence of pyridine; the odor is not enough. We have frequently, in various manipulations with the active substance, met with what we took to be the odor of pyridine, but on shaking out with ether and adding an ethereal solution of hydrochloric acid and evaporating the ether we have been unable to detect pyridine in the residue.

Description of the Tracings.

Fig. 1. Tracing. Dog anæsthetized with morphine; curare and artificial respiration, both vagi cut. Injection of the active sulphate, freed from the carmine substance and coniine-like body, at ×.

a = running base line.

b = time record.

c = curve of the blood-pressure, canula in the right carotid artery.

Fig. 2. Tracing. Conditions of the experiment as in Fig. 1. Injection at × of a highly active sulphate which still gives the rose-carmine color with iodine water and still contains some of the coniine-like substance, which does not raise the blood-pressure. The blood-pressure is so high that the mercury is driven out of the manometer.

Fig. 3. Tracing. Conditions as in 1. Injection at × of a material which is still highly active, although it had been boiled with 5 per cent. sodium hydrate for one hour. In this experiment a number of injections had already been made; the pressure had fallen to the normal before the injection indicated at × was made.

DISCUSSION.

Dr. William Osler: I would like to ask Dr. Abel whether he has examined any of the commercial products of the suprarenal gland on the market with reference to their blood-pressure-raising properties. I have at present two cases of Addison's disease with pronounced vascular asthenia. They have been upon the commercial extract of the suprarenal capsule for some time, but show no effect from it whatever.

Dr. John J. Abel: I have not examined any of the preparations on the market. I think it very likely, however, that they do contain this blood-pressure-raising substance, as it is only necessary to chop up the gland and dry it on the water-bath and powder it in order to obtain an active preparation.

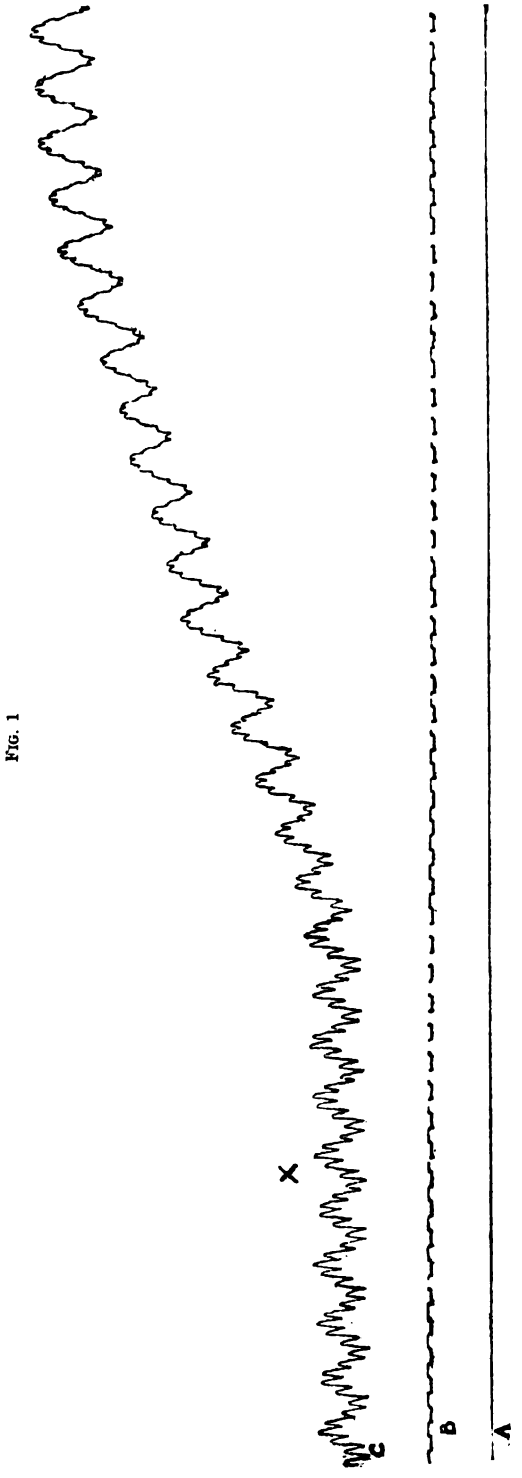


FIG. 1

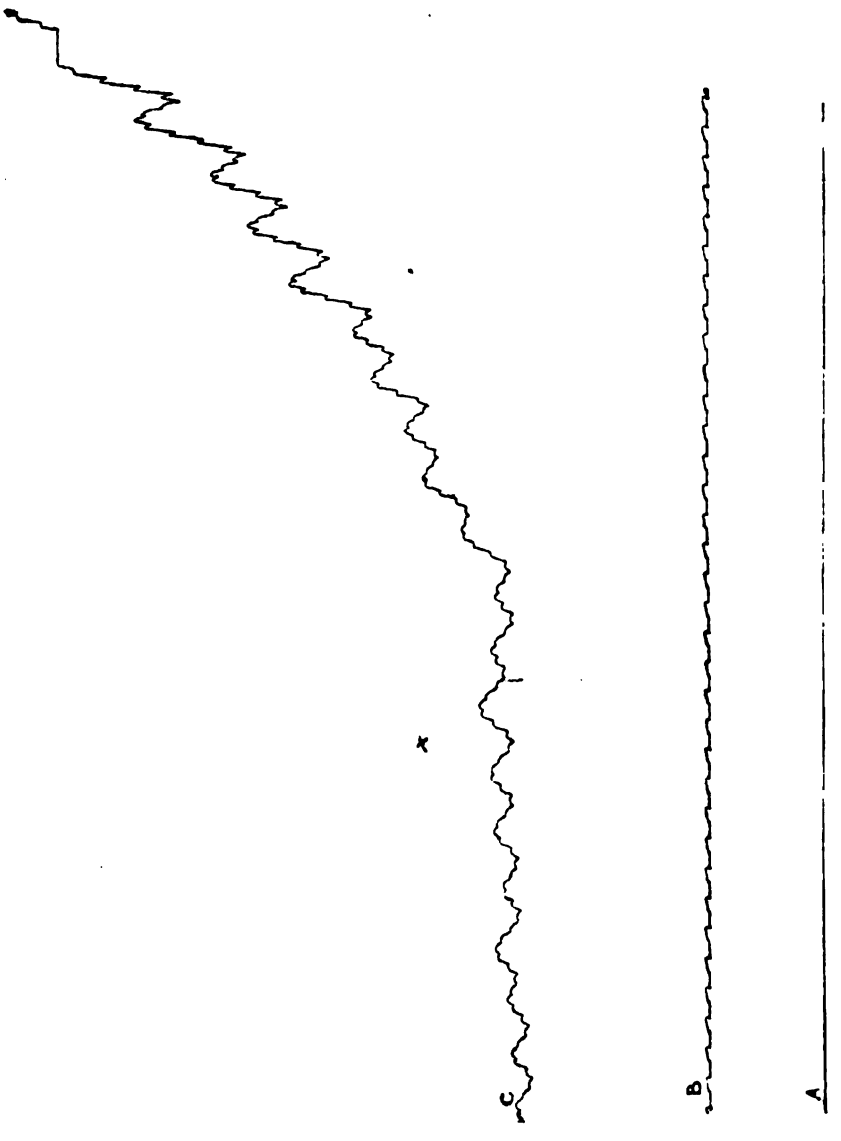


FIG. 2

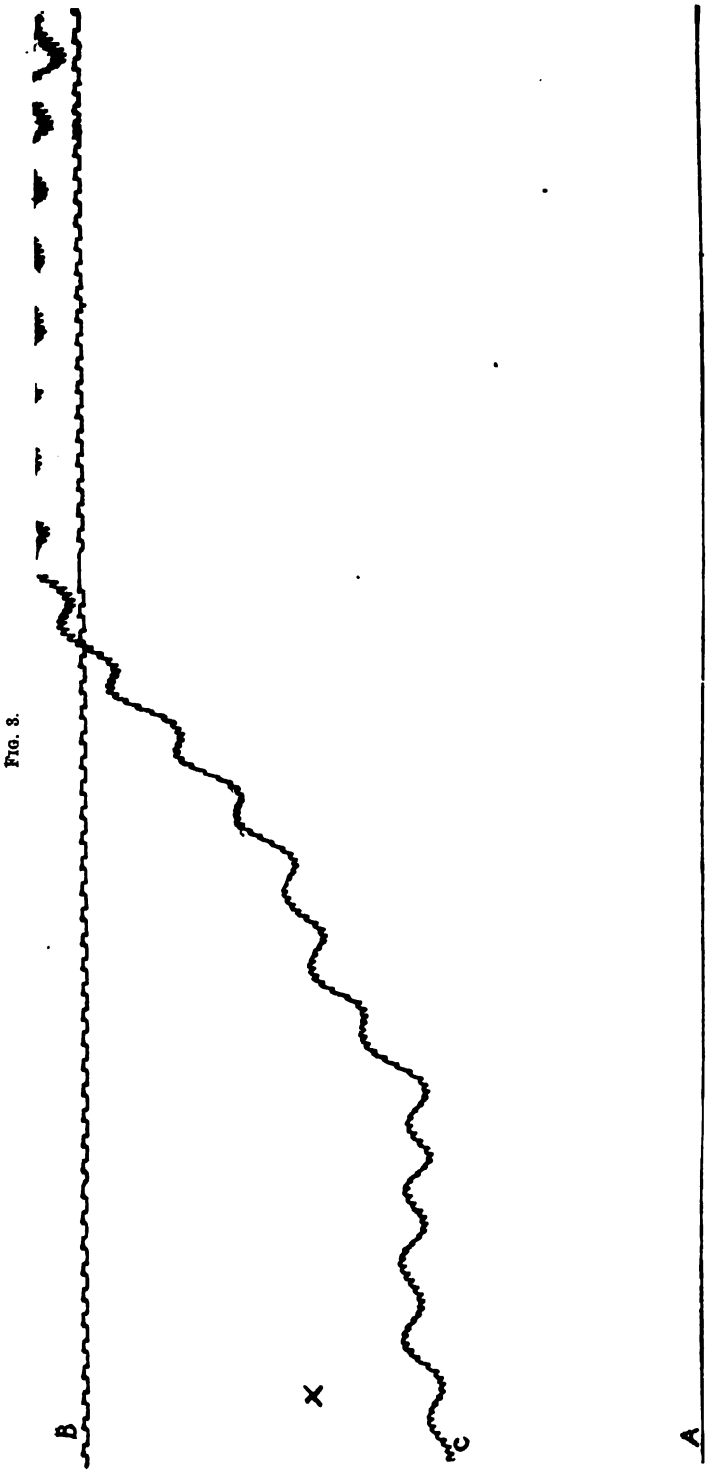


FIG. 3.

AN ANALYSIS OF 3000 CASES OF MELANCHOLIA.

By S. WEIR MITCHELL, M.D.,
OF PHILADELPHIA.

WHILE studying melancholia I observed that certain cases seemed to be apt to relapse in the spring or summer, and I desired to learn if this tendency applied to the onsets of such cases as come but once in a life or to those which repeat themselves at irregular intervals far apart in time.

With these points in view I searched the literature widely, but could obtain no satisfaction beyond vague, general statements. I asked Dr. John B. Chapin, of the Pennsylvania Hospital for the Insane, to let me have a list of dates of admission for melancholias, and I also requested Dr. Robert Chase, of Frankford, and Dr. Henry Hurd, of Johns Hopkins, to give me their views as to the matter. While the results thus obtained are interesting, they show the need for further study.

Dr. Chase writes:

"In reply to your letter of the 24th instant, I hasten to say that in 2220 admissions at Norristown, covering a period of five years (of whom about 30 per cent. were subjects of melancholia), a larger number were received in the months of April, May, and June, and again in August, than during any other months of the year. The smallest number were admitted in October, November, and February. This, I think, conforms quite closely to general statistics on the subject.

"The result of my observation in seasonal recurring melancholia is that relapses are more prevalent in the spring, reaching the maximum in June. This also is in confirmation of statistics respecting suicides, that the wave of accession reaches floodtide in June."

Dr. Hurd writes:

"My impression is that at the North we are more apt to get melancholias in the winter, especially when the vitality of feeble patients has been de-

pressed by unexpected or long-continued cold weather. I remember in a general way when I was in Michigan we always expected a large number of cases of melancholia in the months of January and March.

"As to recurrence of melancholia, I am not able to speak with so much certainty. Recurrent cases do not seem to follow any special law, but develop irregularly."

I give next Dr. Chapin's statement of 680 dates of admission of melancholias to the Pennsylvania Hospital for the Insane:

TABLE I. *Admissions covering a period of thirteen years.*

	Men.	Women.	Total.
January	24	37	61
February	21	39	60
March	28	25	53
April	24	27	51
May	18	41	59
June	25	44	69
July	23	35	58
August	20	36	56
September	22	37	59
October	20	32	52
November	19	32	52
December	16	34	50
Total	260	420	680

Here the numbers teach us little, as a glance at the figures will show. June seems to offer the largest number. So many conditions in the various social classes determine the dates of admission that I am puzzled how usefully to employ these statistics.

Seeing that this table gave no distinct results as to the influence of seasons, I asked permission of Dr. Chapin to have studied the dates assigned for the time of origin, feeling that hospital notes might afford a reasonable approach to accuracy in fixing the time of beginning of the neurosis. They are, of course, liable to many innocent misstatements, and must, I fear, be always open to criticism; but less and less so, as increasing care is given to the matter by the asylum physicians.

Dr. Chapin kindly permitted my assistant, Dr. Pearce, and my stenographer to examine and collect from his books 3037 cases diagnosed as melancholias; 1780 were women, 1257 were men. The time covered lies between 1841 and 1896, as shown in Table II.

TABLE II. *Months of origin of melancholias.*

	1257 Cases Male.	1780 Cases Female.	Combined Cases.
January	79	127	206
February	116	153	269
March	120	151	271
April	118	168	286
May	104	156	260
June	100	166	266
July	106	145	251
August	86	162	248
September	109	115	224
October	93	137	230
November	104	145	249
December	122	155	277
Total	1257	1780	3037

In this list the largest number of male cases is for December, but the numbers vary little except for August, which falls to 86. The largest number of female cases is in April, the smallest in January.

In Table III. the percentages are calculated, and in this shape the comparison is more easily seen.

TABLE III. *Percentage of occurrence of melancholias by months.*

	Male Cases, 1257.	Female Cases, 1780.	Combined, 3037.
January	6.285	7.135	6.783
February	9.229	8.595	8.857
March	9.547	8 483	8.923
April	9.338	9.438	9.417
May	8.228	8.764	8.567
June	7.956	9.326	8.758
July	8.448	8.146	8.251
August	6.845	9.101	8.166
September	8.625	6.461	7.385
October	7.399	7.697	7.573
November	8.288	8.146	8.199
December	9.702	8.708	9.121

April gives, of the total men and women, 9.417 per cent., and December comes next—9.121 per cent. Too much may be made of such a table. It serves to make clear, however, how very small is the difference of time of origin. The late winter and early spring months seem to offer most cases. I confess myself surprised at the want of more differing results for the several seasons.

While thus employed my assistants took note of some other matters which proved to be quite worth this trouble. One was a table, which I do not print, of the causes assigned as parents of melancholia. This table satisfies me that some very carefully planned measure is needed to bring this matter into useful form.

I am told that the Psychological Society of North America has a committee thus engaged, and, with this knowledge, to criticise would be unnecessary and without useful end.

An effort was made to state the duration of melancholias in 422 cases where the time was noted, and Table IV. shows the continuance of the disorder previous to admission, as stated by the friends. This statement as it stands is a strange record, and appears to show how many cases remained at large after the onset of the disease before they were placed in the institution. Possibly a large percentage had been in other asylums, and the table has no serious value.

TABLE IV. *Duration of attack at time of admission.*

	Males.	Females.
One month or over	1	0
Six months	2	2
One year	88	83
Thirteen months	0	1
Fifteen months	0	1
Eighteen months	6	8
Two years	44	51
Two and one-half years	8	1
Three years	26	19
Three and one-half years	2	1
Four years	6	16
Five years	9	8
Six years	6	8
Seven years	0	1
Eight years	3	1
Nine years	1	0
Ten years	3	5
Thirteen years	0	1
Fifteen years	2	0
Sixteen years	1	0
Twenty years	2	0
Twenty-two years	0	1
Twenty-four years	0	1
Twenty-six years	0	1
Thirty years	1	0
Thirty-one years (case of trauma)	1	0

TABLE V. *Comparative percentage of cases by decades.*

	Male.	Female.
Under twenty years	$3\frac{7}{10}$	$6\frac{1}{5}$
Between twenty and thirty years	$26\frac{4}{5}$	$26\frac{2}{5}$
Between thirty and forty years	$27\frac{3}{5}$	27
Between forty and fifty years	$20\frac{1}{5}$	$21\frac{2}{5}$
Between fifty and sixty years	15	$14\frac{1}{5}$
Between sixty and seventy years	$5\frac{2}{5}$	$4\frac{1}{5}$
Over seventy years	$1\frac{3}{10}$	$\frac{3}{5}$

This comparison of ages is most striking, and the correspondence in age in the two sexes is well worth attention. The cases in both sexes might have been better grouped, so as to bring out the influence of the menopause; nevertheless, even as at present arranged it is valuable, and confirms statements from other asylums; also it leads to the observation that in men the percentage between forty and fifty years is $20\frac{1}{5}$, and in women but $21\frac{2}{5}$. Or, if we take the years from fifty to sixty, the percentage of male cases would be 15, and of female cases $14\frac{1}{5}$. These two sets of figures seem to dispose of the idea that women are more liable to melancholia at or about this critical period. But in order to get at this even more precisely I had the percentage calculated for the years from forty-five to fifty-five, with a result which shows practically no difference from the statement for the decade from forty to fifty.

Again, if we consider the whole table, it would appear that the time of greatest liability is for both sexes between twenty and sixty years, but under twenty it is relatively nearly double for women.

In further confirmation of the fallacy of attributing melancholia to the menopause, I append some statistics furnished by Dr. Ely Josselyn, of the Pennsylvania Hospital for the Insane.

New York State Lunacy Report, Table III., p. 526.

From 1888 to 1894 there were 16,208 admissions, of which 7475 were women. Of this number, 282 cases were attributed to the menopause—less than 4 per cent.

In five asylums in Massachusetts, Worcester, Taunton, Northampton, Danvers, Westborough, we note the following:

In 1895–'96.

Worcester 292 admissions, of which twelve were attributed to the menopause—4 per cent.

Taunton 209 admissions; three attributed to the menopause—less than 2 per cent.

Northampton ninety-four admissions; two attributed to menopause—less than 3 per cent.

Danvers 218 admissions; seven attributed to the menopause—less than 4 per cent.

Westborough 276 admissions; four attributed to the menopause—less than 2 per cent.

At McLean Hospital, of sixty-three admissions two were attributed to the menopause—less than 3 per cent.

In the Connecticut Hospital for the Insane since its opening, in 1868, of 3607 admissions eighty-six were attributed to the menopause—less than 3 per cent.

In the reference above it is clearly shown that of all insanities recorded in these institutions only about 2 per cent. were attributed to the menopause. If this obtains in general insanities, the question arises how large a factor the climacteric is in melancholias alone.

Through the kindness of Dr. Moulton, of the Pennsylvania Hospital for the Insane, I append the following extract from the *United States Tenth Census Report:*

Of the 27,105 cases of insanity tabulated by the Tenth Census, there was one male lunatic to 574 persons, and one female lunatic to 518 persons.

While this would seem to contradict the assertion that more men are insane than women, it must be remembered that more men die of paresis than women. More women are found in hospitals than men because not many female cases are fatal.

In seven hospitals in Massachusetts (a State where there are more women than men in the general population) out of 63,525 people the commitment of men exceeded that of women by 605.

TABLE VI. *Number of cases having had prior attacks*—672.

	Male.	Female.
One prior attack	168	277
Two prior attacks	38	99
Three prior attacks	18	28
Four prior attacks	11	15
Five prior attacks	3	4
Six prior attacks	2	0
Seven prior attacks	2	0
Eight prior attacks	2	0
Nine prior attacks	2	1
Ten prior attacks	0	0
Eleven prior attacks	0	0
Twelve prior attacks	0	0
Thirteen prior attacks	0	1
Total	246	426

I felt too doubtful of the value of these statements to think it worth while to work out the percentages. Females seem more liable to recurrence of attacks than men.

Of the number of cases under consideration (3037) the age was given in 2547 instances, and the averages are given in the following table:

TABLE VII. *Age of occurrence of melancholias.*

Average age of males	37⅛
Average age of females	36¼
Oldest male case	76
Oldest female case	78
Youngest male case	10
Youngest female case	12

Considering the very different conditions under which the lives of the two sexes are passed, this close relation as to time of liability to attacks is interesting.

I thought some of the points made plain by these tables valuable enough to make it worth while to print them; but I have been cautious about inferences, and should like to see what I have attempted worked out on a larger scale by the publication of the records of a number of hospitals, and for all the distinct types of insanity.

I have the privilege of using my friend Dr. John B. Chapin's valuable comments on these tables. These relieve me from the need to say anything further; they are of remarkable interest. Dr. Chapin says: "I hardly like to venture any criticism, or even to make suggestions, about a work on which you have expended so much time.

"As for the table showing the seasons at which melancholias make their appearance, I think it is, as you say, negative of all results, except in showing that there is no 'seasonal melancholia.'

"As to the date of attack, the hospital and the physician preparing the certificates for admission depend mainly for the history of the case upon the friends of the patient, only some of whom are intelligent, and even these are often not correct observers. Therefore, the date of the insanity is usually fixed at the time some open manifestation takes place, and no account is taken of the incipiency which may have been in operation for months. As your tables are the first contribution in the line of this inquiry, they must be accepted as of

authority, although it should be remembered that they are based largely upon the admissions to a hospital receiving patients from a city population in the latitude of Philadelphia. The dates which make up your table are all that are accessible for this locality.

"I entirely agree with you about the small value the table of assigned causes has in this relation. I have never attached any importance to any table of this character that I have seen published. It is usual to enter in the case-book the 'assigned cause' of insanity furnished by the friends as a part of the history of the case. It is not always the cause which the physician would assign. To estimate the cause of any insanity is such a complex operation that sufficient time cannot be given to the analysis of every case to make the results of value. For my own convenience I have sometimes made a classification depending upon whether the disease was supposed to be recoverable or irrecoverable; whether acquired or due to organic degeneration.

"Table IV. is valuable as showing approximately how long such patients are at large before admission to an institution. It is useful, too, in giving some idea of the duration of the disease, and it is again the only information obtainable in this direction.

"Table V. I consider the most valuable contribution to knowledge which your paper furnishes. In the first place, you have established by Table II. that more men are sent to hospitals with melancholia than women, and it is true that more men become insane than women.

"The estimation of the occurrence of melancholia in the years between forty-five and fifty-five shows that the climacteric period, which all women dread who have a predisposition to insanity or to any neurosis, exerts but little influence upon this condition; an equal number of men and women become insane at this period. In this connection I may remark that the expectation that insane women are to recover at the climacteric period is equally fallacious. This fact, which I am not able to verify by statistics, is difficult to prove, but I am quite assured of its truth from observation, and you may as well explode the tradition as anyone else. The decades following fifty show an increased percentage for men, and this might be expected, as the known fact is that more men become insane than women. The facts shown by this table are worth all of the labor you have bestowed upon your paper."

THE EFFECTS OF VARIOUS METALS AND METALLIC SALTS ON THE GROWTH OF BACTERIA.

A CONTINUATION OF EXPERIMENTS PRESENTED MAY 30, 1894.

BY B. MEADE BOLTON, M.D., AND W. G. BROWN, M.D.,
OF COLUMBIA, MO.

IN a paper read by one of us before this Association three years ago, attention was called to the fact that peculiar zones are formed around bits of metals of various kinds laid upon thickly sown plates of bacteria. In all the substances that were tested, except carbon and silicon, there is a wider or smaller zone in which no bacteria grow, followed by zones more or less peculiar to the kind of metal and the kind of micro-organism in which the growth of the bacteria is present, or even apparently increased, followed sometimes by a zone in which growth is hindered to a greater or less extent. In some cases there may be several alternating zones of increased and of diminished growth, or even absence of growth. The reason for this peculiar behavior of the micro-organisms was not apparent at the time, and we have endeavored in the following experiments to find an explanation. We have also tested the point as to whether metallic salts cause the bacteria to behave in the same way as the metals themselves do. Another question that has received attention is whether the zones in which the bacteria show intensification are due to an increase of the number of colonies or to an increase in the size of the individual colonies.

In all of our experiments we have used cultures of the anthrax bacillus, and in most of them we have used mercury and its salts and cadmium and its salts. But in addition to these we have also tried salts of iron, zinc, nickel, copper, and iodine, and iodide of potassium. Moreover, various combinations of metals and salts were tested.

The plates were made in the usual way by inoculating the melted medium, and after it was poured out and allowed to cool the metal or salt to be tested was laid on the surface. Plates were also made containing no bacteria, simply with the metals and salts laid on the surface. Again, other plates were made containing various amounts of the metallic salts in solution. These were made to test whether the presence of very small quantities of the salts causes a stimulation of growth.

As was to be expected, the salts of the metals have essentially the same effect upon the bacteria as the metals themselves, and this effect is in direct proportion to the solubility of the salt. Where the medium is prepared with a small amount of a metallic salt in solution and a piece of metal is laid on the surface, the effect is enhanced. Thus in a plate of agar containing mercuric chloride in the proportion of 1 to 40,000, with a bit of cadmium placed on it, the zone of inhibition around the bit of metal is much wider than on a plate where there is none of the mercuric salt and only the bit of cadmium (see illustration on page 491, *c* and *d*).

The explanation of the behavior of the bacteria became very evident from the observation of the distribution of the metals and their salts in the agar on plates sown with bacteria, as well as on uninoculated plates, for the metallic salts themselves tend to accumulate in one or more concentric zones around the spot where the salt is laid. So great is this tendency of the salts to creep away from the centre and accumulate in zones that sometimes there is actually less of the salt at the spot where it was originally deposited than in some of the zones at quite a distance from this spot. Indeed, where there is a very small piece of the salt put on, it may almost disappear from its original situation. This tendency of a salt to form its zones can be strikingly brought out by making a solution and placing a drop on filter-paper. If a drop of a solution of cadmium sulphate is placed on a bit of filter-paper and the filter-paper exposed to an atmosphere of sulphuretted hydrogen, there will be found a deep orange zone some distance from the point at which the solution is dropped on, and within this ring there is often little or no color, showing that the salt has crept out to the periphery of the space that is made wet with the solution. Moreover, plates of agar that have had bits of cadmium, or of a cadmium salt, placed on them, when exposed to an atmosphere

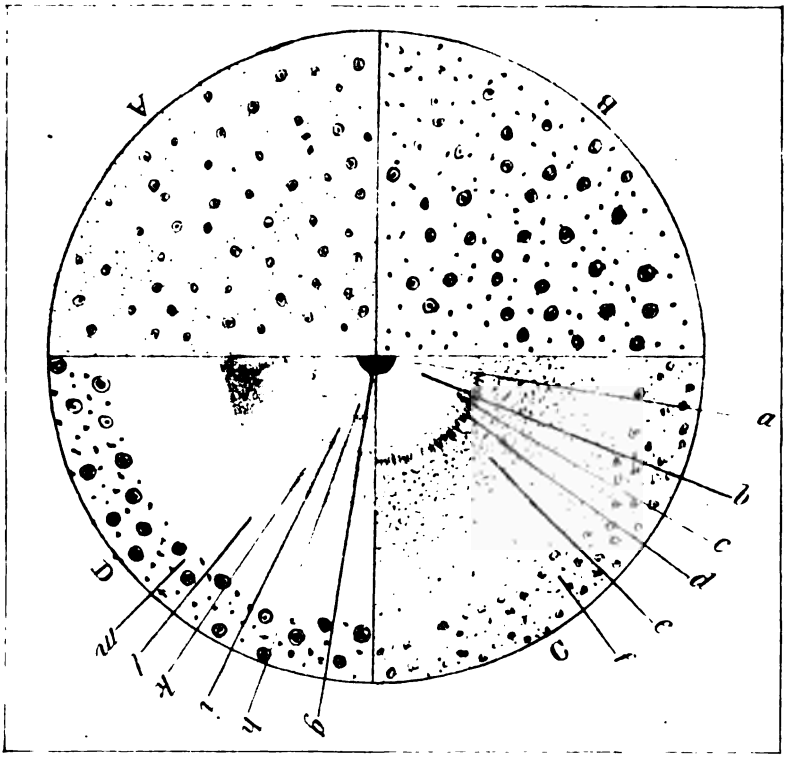
of sulphuretted hydrogen show the same zone or zones as seen on filter-paper. So that there can be no question that the zones of growth of the bacteria are determined by the distribution of the metallic salt. By close observation it can be actually seen in agar plates of anthrax upon which a bit of cadmium is laid that there are zones in which the metal has accumulated and that in these zones there are few colonies of anthrax or none. The zones of inhibited growth correspond exactly with the zones of concentration of the metal, and the zones where the bacteria are most abundant will be seen to be free from the metal (see illustration, *c*). Now, in the space surrounding the original location of the metal there is frequently an absence of metal as well as of the bacteria; but this can be explained by supposing that in travelling out the salt destroyed all the bacteria in its path.

As already stated, frequently just outside and just inside the zone of greatest concentration of the metal there are zones where there is an intensification of growth. It is possible that this intensification might be due to an increase in the number of colonies over that found elsewhere on the plate, or it might be due to an increased size of the individual colonies. And the latter is the correct explanation. Usually in the intensified zones there are actually fewer colonies than elsewhere on the plate, and their larger size may be due simply to the fact that they have more room in which to grow. While it seems probable that this is the explanation of the increased size of the colonies, it also appears, in some cases at least, that there is a stimulation of growth.

A large number of experiments made to test whether a very small amount of salt has the effect of stimulating growth have left us still somewhat in doubt. We are inclined to think that although stimulation takes place in some cases, it does not always occur. In experiments made by adding traces of an iron salt to the medium there was a decided increase in the size of the colonies over those in the ordinary medium containing none of the salt. In similar tests made with salts of mercury and of cadmium this effect was, to say the least, not always apparent; but in the plates from which the accompanying illustration was made there appeared to be decided stimulation.

The illustration on the next page represents segments of four different Petri plates of anthrax. One of them, A, was a plate made in the

usual way without the addition of any metal or salt, and serves as a control-plate. One of them, B, contained corrosive sublimate in the proportion of 1 : 40,000. One of them, C, made as A, had a piece of cadmium, *a*, placed in the centre. One of them, D, contained corrosive sublimate in the proportion of 1 : 40,000, made as B, and in



A, segment of a Petri dish culture of the anthrax bacillus in ordinary nutrient agar; B, the same with the addition of 1 : 40,000 of corrosive sublimate; C, the same as A, but with a piece of cadmium placed in the middle; D, the same as B, but with a piece of cadmium placed in the middle

addition had placed on it in the centre a piece of metallic cadmium, *g*. Plate C, made in the usual way, but with a bit of cadmium (*a*) placed on the centre, showed the usual zones, namely, a clear zone (*b*) around the metal, followed by a narrow zone (*c*) containing colonies; then a zone (*d*) free from colonies, but showing a narrow striated band

of metallic lustre; then a wide zone containing a number of colonies, but none on the surface, the growth being intensified in the portion nearest the centre; lastly, a zone (*f*) not differing from the control-plate, A, in any marked degree. Plate D, containing corrosive sublimate in the proportion of 1:40,000, and, moreover, a bit of cadmium (*g*), showed no colonies of bacteria except in the peripheral zone (*m*). This zone was about as wide as zone *f* of Plate C, and was similar, except that there were fewer colonies and these were larger. There was a wide zone (*l*) that was perfectly clear, showing neither colonies nor metal. Around the bit of metal (*g*) there were three zones (*h, i, k*), showing the presence of the metal by the discoloration of the medium. These three zones were all similar in appearance, but zone *i* differed from *h* and *k* in being less dense.

From these plates it is evident that the colonies are larger in Plates B and D, containing a minute quantity of corrosive sublimate, than in the control-plate A, but it cannot be decided with certainty whether the increased size of the colonies is due to stimulation of the salt or to there being fewer colonies, and hence more space around each colony for growth, or to both causes. We are inclined to think that both of these may be factors. The corrosive sublimate may have destroyed the weaker organisms and given a stimulus to the survivors.

The tendency of the cadmium to accumulate in zones is shown in C at *d*, and in D at *h* and *k*. It is also evident from Plate C that the surface-growth is more affected than the growth under the surface.

JACKSONIAN EPILEPSY: ADENOMA OF LIVER; ACUTE ASCITES WITH TUBERCLE BACILLI.

By A. JACOBI, M.D.,
OF NEW YORK.

A. A. was born August 7, 1885, and died January 16, 1897. Her father was always in good health, her mother at one period of her life neurotic. Father's family was without any morbid taint; mother's ancestors died when seventy-five, eighty-five, and ninety years old. She is the youngest of ten boys and girls, none of whom died young. One sister died of cerebro-spinal meningitis, one of "fistula" after having been insane, one brother (the oldest in the family) was an army officer during the civil war and died insane. Of the seven now alive one, a man of great abstract learning and a college professor, with healthy children, is epileptic.

A. A. weighed eight pounds at birth, sixteen when six weeks, twenty-eight when ten months old. Her first teeth (lower incisors) appeared at six months; the others, both temporary and permanent, came in due order and without any trouble. She walked when a year old. She was wet-nursed, never perspired on the head, lost no hair, had no thickened epiphyses, her limbs were straight. The only symptom reminding of rickets was constipation, which appeared at the age of six or eight weeks, and required enemata until she was five years old. At three years of age she had whooping-cough; at four, measles; no other disease.

In September, 1891, she fell from a swing, hurting the left side of her head. She did not get pale nor vomit; she cried, and appeared uninjured. In January or February, 1892, her right hand was noticed to twitch a little. In November she began to take music lessons, the twitching became stronger and more frequent, and the lessons were discontinued. On the first of November, 1893, she had on waking in the morning the first hard attack of convulsions, probably with loss of consciousness. The second attack of the kind took place on the 16th. There was complete loss of consciousness and slow recovery. Thick, incoherent talk; slight paralysis of the right arm. During two days previously the child, who was remarkably observing and intelligent, had noticed fatigue and pain in her right arm, and told a playmate she was going to have an attack. On November 24th she complained of tiredness and numbness in both arms, more so in the left. She slept poorly during that night, and experienced slight twitchings in her right hand. Feeling

an attack coming on at 6.30 A.M., she jumped up with the idea of preventing it. It was slight, with no loss of consciousness. Slight stiffness of legs. She said she had to hold on to the foot of her bed, as she was not quite steady. Afterward she felt absolutely well, and played all day. Had taken bromides two days; they were continued in moderate, and later on in larger doses, so as to give rise to bromism repeatedly. Slight twitchings of the right arm in the night of February 18, 1894. March 9th, while running, she tripped and fell, striking her right arm heavily. She complained at once of twitchings, which, though slight, continued over an hour. She was put to bed, but she complained of their coming more frequently while she was lying down; tying a cord round the arm above the elbow made the twitchings stronger. She seemed very nervous and worried each time the arm twitched. When she was read to the shaking stopped instantly, and she was well all day. Evidently this attack had but partly the significance of the former ones. Right arm shook badly on waking April 4th, after she had been playing, skating, and falling several times the previous afternoon; again on April 13th and May 22d. During two days previously she had complained of fatigue and pain of her left hand. She had been writing a good deal, however, with her left hand previously, having been taught and accustomed to use her left hand in place of the right when the local convulsions began. Slight attack on the 27th, two on June 2d.

Most of the attacks would come on in the morning on waking up; they lasted mostly a few minutes, and were but rarely attended with unconsciousness. She would often laugh and joke immediately afterward. During most of the attacks, and often days before, the child was pale; sometimes she was irritable before or after them, in some instances for days. But very few times she had more severe attacks during her sleep, breathing heavily and shaking all over her body. Before she was taken to Europe in the summer of 1894, she had, however, only very few of these hard attacks. Up to this time, and also later, she enjoyed the occasional advice of Dr. S. Weir Mitchell, who saw her both in Philadelphia and in New York. Drs. Gowers and Jackson saw her in London. It was principally the former who objected strenuously to the performance of an operation the advisability of which had been suggested.

During her European trip she was not changed. Slight attacks would come mainly when she was, or had been, fatigued; five during August, 1894. After three slight ones, on her return, she had a fully developed epileptic attack in her sleep on October 26th. After a few slight ones, in January, 1895, the attacks ceased entirely while she was taking, first fifty, afterward sixty grains of bromides daily, together with lithia and valerianate of zinc. The bromides having disagreeable effects (as heaviness, drowsiness, bloated face), were discontinued June 8th, and valerianate of zinc only administered. Attacks returned—one on the 25th, two the 26th, three the 27th, four the 28th, six the 29th, four the 30th (wetted the bed the first time), six on July 1st (was given again bromides, grs. 60 daily, zinc valerian., 30 grs., atropia

gr. $\frac{1}{120}$), six on the 2d and on the 3d, nine on the 4th and on the 5th, five on the 6th, and three on the 7th. The bromides again showing a disagreeable effect, they were diminished, and the daily medication consisted of 30 grains of the bromides, 15 grains of valerianate of zinc, 10 grains of zinc oxide, and $\frac{1}{30}$ grain of atropia.

No attacks until December 21st (slight) and 22d (hard), after which she was given 60–70 grains of bromides daily, and 30 grains of valerianate of zinc, for one week. They were then stopped awhile; the attending physician, who saw her often every day, changing the medication as circumstances appeared to demand.

During 1896 the case changed for the worse. There was a severe convulsion on January 2d; it began in the right arm, and was mostly confined to the right side. Unconsciousness lasted but a few minutes, but there were great weakness and numbness of the right arm. It is quite important to remark that her intellectual faculties suffered very much less than the arm from an attack.. On the 3d there was a severe local convulsion of the right arm without any unconsciousness, and one slight attack on the 15th, 16th, 18th (two attacks), and the 20th. On the previous night her pallor was excessive and her pulse feeble. In February she had twenty-one attacks of shaking or twitching of the right arm (one of the fingers of the right hand only) on ten days altogether. During March, 1896, the attacks, all of them localized, no general convulsions, became both more numerous and more severe. She had four on the 1st, five on the 2d, three on the 3d, 4th, 5th each, four on the 6th and 7th each, six on the 8th and 9th each, seven on the 10th, eleven on the 11th, fourteen on the 12th, twenty-seven on the 13th, twenty-six on the 14th, twenty-nine on the 15th, forty-nine on the 16th, twenty-five in the night of the 17th, twenty-six on the 18th between 7 A.M. and 9 P.M., twenty-eight on the 19th during the same hours, and nineteen in the following night. The last few days many of these local convulsions were attended with heavy breathing, the body was often drawn to the left while the right arm was drawn up or shaking, or both, and on the 19th the mouth was noticed to be drawn to the left.

It was on that day that Dr. Charles A. Dana saw the patient. To his kindness is due the following report:

"The patient was seen by me March 19, 1896. She was a well-grown girl for her years, and apparently well-nourished, but quite anæmic. Her mind was particularly bright and mature. She had a slight weakness of the right arm, but no paresis of the facial muscles or of the legs. The knee-jerks on both sides were normal, not exaggerated on the right side. The right arm showed a certain amount of ataxia. There was an inability to place the finger easily on the tip of the nose with the eyes closed, or perform delicate muscular movements, such as buttoning the clothes or picking up small objects from the table. There was also a slight lack of localization sense, so that she could not determine exactly the point touched by the hand or arm. There was, however, absolutely no anæsthesia, tactile, pathic, or temperature

anæsthesia. The elbow-jerk was present. There was no atrophy or any tremor or spasmodic movement in the arm. The tongue protruded straight, and there was no asymmetry of the facial muscles. The patient had no concentric limitation of the visual field or aural field, no loss of sense of smell or taste, no pharyngeal anæsthesia; in fact, absolutely none of the stigmata of hysteria. There was simply the weakness of the arm, with ataxia and defect in "motor touch," such as is found in disease of the motor cortex. During the examination she had several slight convulsive attacks; the arm was extended, the forearm pronated, the hand flexed, and the whole arm raised out somewhat from the side. The head was drawn over, to some extent, to the same side; but the eyes did not move. There was some twitching of the muscles of the face of both sides. There was no biting of the tongue, and had not been. The attack came on suddenly, and without cry or distinct aura; the patient asserted that it was not accompanied by loss of consciousness. It lasted only one or two minutes. After it was over the arm was, for a time, almost paralyzed, but after a few hours gained considerable strength. She would have a number of these attacks during the day. Shortly after my visits began they ceased, however, and the arm grew gradually stronger, less clumsy, and eventually she could use it nearly as well as the left, though never quite the same.

"The attacks were quite typical examples of a Jacksonian epilepsy. She had had at no time any severe headaches, no vomiting, and had no optic neuritis. The diagnosis at the time was Jacksonian epilepsy, due probably to some slight degenerative changes in a limited area of the motor cortex."

Under the direction of Dr. Dana she took on March 20th nitroglycerin, gr. $\frac{1}{200}$, and urethan, grs. 5, every two hours, bromides, grs. 50, through the day. She had thirteen severe attacks through the day (they had since becoming so numerous been more frequent during the day), and nine in the night; on the 21st forty-five and fifteen (bromides grs. 45, urethan grs. 45, nitroglycerin 6 tablets of $\frac{1}{200}$ gr.); on the 22d thirteen hard attacks and thirty-three slight twitchings from 6 A.M. to 10 P.M.; six times the right leg shook with the arm. There were four slight attacks in the following night (medication, bromides grs. 35, urethan grs. 50, tablets No. 7). On the 23d there were forty-nine slight twitchings between 8.30 A.M. and 10 P.M.; none in the night. Medication, bromides grs. 30, urethan grs. 55, tablets No. 3. The child was much brighter and stronger. On the 24th there were twenty-one slight twitchings between 7.30 A.M. and 9.30 P.M. Medication, bromides grs. 30, urethan grs. 60. On March 25th and the following days the same medication and no attack whatsoever at any time. On April 1st albuminuria was noticed, and urethan was given in doses of 45 grains; on the 3d less albumin, urethan 30 grains. This dose was continued. On the 6th there was hardly a trace of albumin, and the appetite good. At the same time daily doses of 30 grains of bromide were given; from July 5th to July 11th she took 25, after that 20 grains daily.

It should be here remarked that during the time of the greatest number and severity of the attacks large doses of bromides, up to 100 or even 120 grains,

were given daily, together with, or without, the valerianate of zinc, and had often to be discontinued because of serious bromism. The only time in which the *attacks ceased and the patient felt better at the same time was when she took urethan.*

She continued this medication while in the Catskill Mountains all summer, 1896. Her general condition did not improve; she lost flesh and was pale, though in fairly good spirits most of the time. The amount of albumin in her urine, which was considerable while she was having her attacks, diminished. But while there was hardly a trace and sometimes none in the middle of the summer, there was constantly a small quantity of bile in the urine. In October I saw her. She was in bed, pale (she *never was icteric*), with anorexia and a frequent pulse. She improved somewhat until in November she felt better, took drives, and with slight support once walked ten blocks. Then her general condition, however, changed for the worse, without any fever or other tangible symptoms. I saw her with Dr. Dana on December 1st. During that month she grew thinner and paler. On December 28th her nurse noticed some swelling of the abdomen, which had been rather sunk and lean. That swelling was observed plainly by the mother and by Dr. Dana on January 2, 1897. It was considered to be due to obstruction of the bowels; a high enema brought away a peculiar substance, mixed with some blood, of greenish color and offensive odor. The temperature was but slightly raised, and there was no pain. Within one or two days the abdominal cavity filled up with fluid, the diaphragm was somewhat impeded in its motion, respirations increased to thirty and thirty-six. No anasarca, no local œdema anywhere. The abdominal veins were very numerous and dilated, but no caput Medusæ.

A few days afterward her (moderate) dyspnœa became a little less annoying; the abdomen appeared a little less tense, and the veins somewhat smaller. Still this apparent temporary improvement did not last, and in a very few days the general condition suggested the necessity of an operation the beginning of which was to be a laparotomy. Dr. McBurney joined Dr. Dana and me in a consultation. The suddenness of the abdominal effusion suggested the presence of a thrombosis of the portal vein, or the presence of a tumor of some kind, perhaps tuberculous lymph-bodies, compressing the portal vein. The spleen had been made out to be large the previous week; the liver appeared somewhat swollen. Some solid or semi-solid masses could now and then be felt, but we could not be certain whether we had to deal with normal or inflamed and adherent intestines or neoplastic growths, or peritonitic exudations. During all this time her strength gave way slowly, with very poor appetite and a urine which, after having been copious, became scanty and dark. In the last few weeks its specific gravity ranged from 1025 to 1033, its urea about 0.031 in 1 c.cm. There was a faint trace of albumin, no sugar, little oxalate of lime, very little bile, a large amount of urates and phosphates, some bladder epithelium, and some little pus and mucus.

Laparotomy was performed by Dr. McBurney on the 10th. There was a

gallon or more of a thin, yellowish fluid in the abdominal cavity. Its specific gravity was 1011; it contained but little albumin and few salts. These examinations were made of specimens of fluid which were removed when the discharge was about half finished. The spleen was found to be large, the liver of moderate size, there were no adhesions between the intestines or between them and the abdominal wall or the viscera. No large neoplasms. The omentum was in good condition, the mesenteric glands were not swollen; the glands surrounding the portal veins were felt to be enlarged, so as to form a thick mass encircling and pressing on the portal vein.

The surface of the liver was shining and covered with very numerous yellowish-gray bodies. They were of different sizes, from the head of a pin to that of a bean. Those of the latter size were felt reaching far down into the liver tissue. They were taken to be tuberculous.

Many specimens of the abdominal fluids were centrifuged and stained, and examined for tubercle bacilli or other microbes. One in six such specimens yielded *large quantities of bacilli tuberculosis* in close proximity to each other.

The general condition of the patient did not improve after the operation. Her axillary temperature was never over 100.8° in the axilla, usually 100° or less, down to 98.8°; the respiration remained between thirty and thirty-six; her pulse rose until on the day of her death, January 16th, it reached 158, but little influenced by stimulant subcutaneous injections, which were continued until about twelve hours before she died.

The autopsy was made on January 17, 1897, twenty-four hours after death, by Dr. James Ewing. The following report is mostly from his pen. By his painstaking investigations extending over many weeks he has placed me under lasting obligations.

REPORT OF AUTOPSY.—Body that of a moderately well nourished, distinctly anæmic child. Rigor mortis slight. No œdema or jaundice.

Heart. Pericardium normal. Right chambers moderately distended with clotted blood. Left chambers contracted, nearly empty. Valves, muscle, endocardium normal. No dilatation or hypertrophy.

Lungs. Show considerable venous congestion and œdema. Bronchial nodes deeply pigmented, not tuberculous. Pleural cavities contain a few drachms of serous fluid.

Peritoneum. Intestinal walls uniformly anæmic, peritoneal coat is slightly dull and in places granular. In pelvic cavity, about drainage-tube, are a few drops of pus, and a light purulent coating over adjacent coils of intestine. Parietal peritoneum shows evidences of intense venous congestion, presenting large patches of superficial dark and bloody infiltration. No miliary tubercles were anywhere seen, after close scrutiny.

Liver. Size about normal; surface and section dotted with very numerous light yellow nodules, from pin-head to pea-sized, very sharply outlined from the surrounding tissue. Some of these nodules project slightly above peritoneal surface. They are not caseous, but otherwise closely resemble miliary tubercles. There are many less on the surface than in the interior. The

hepatic tissue shows very distinctly the gross appearances of chronic congestion, the centres of the lobules being very deep red and depressed, the peripheries very light colored, but no blood oozes from the sections.

Gall-bladder. Contents and mucosa appear normal.

Spleen. Considerably enlarged, four to five inches long, consistence firm. On section the Malpighian bodies appeared very prominently set off from the deeply congested pulp tissue.

Kidneys show moderate venous congestion, but are otherwise normal. Adrenals normal. Pancreas normal. There is marked superficial congestion of ovaries, otherwise the genital organs are normal.

Intestinal mucous membrane appears normal. The solitary follicles are only faintly visible. The stomach is moderately congested and coated with mucus.

On opening the peritoneal cavity attention was at once directed to the condition of the portal vein. The gastro-hepatic omentum was found much thickened and very firm, the enlargement proving on dissection to be due to swelling of the periportal lymph nodes, four or five of which, measuring from 5 to 1 cm. in diameter, formed a nearly continuous mass along the portal vein. Undoubtedly these nodes during life produced considerable narrowing of the lumen of the vein. On removing the liver and a portion of the diaphragm, an enlarged lymph node, measuring 1 x 1½ cm., was found lying immediately above and adherent to the hepatic vein at its junction with the vena cava. It was hard, and its capsule covered with large veins, so as to look almost angiomatous. It did not seem possible that the hepatic vein could have escaped partial compression by this considerable mass of tissue. On section these lymph nodes appeared deeply congested, but not tubercular. No thrombi were found in either the portal or hepatic veins. The mesenteric nodes were not enlarged.

Brain rather large, the convolutions not flattened. Pia mater was opaque, whitish, thickened, and rather hard over a large surface; moderately congested, mostly so over the region of the motor centres. This change was more perceptible on the left side than on the right. In this neighborhood the convolutions were rather separated from each other and felt hard. This condition was suggestive of interstitial swelling in the white substance. The structure of the brain appeared normal everywhere, the ventricles were empty, the plexuses normal.

The left half of the *cranium* was smaller and flatter than the right.

Over the left motor centre there was a defect in the structure of the bone, 1¼ cm. wide and 2¼ cm. long, in a forward and downward direction. The bone was translucent, its outer surface quite smooth and on a level with the rest of the cranium, its inner surface depressed. This depression was quite sharp, as in craniotabic defects. There were two more such defects on the same left side, in a forward direction, quite as wide but shorter, about 3 cm. from the median line. One more such spot was found over the left brow; another was located over the left motor centre, 1½ cm. long and 1½ cm. wide. The space of the large fontanelle, 2½ by 3 cm., was occupied by hard, thick, and rather irregular

bone, which was surrounded by a narrow (about ¾ cm.) semi-transparent area. To the left of this, and rather forward and adjoining the coronal suture, was a triangular osseous island, also flanked by a transparent area.

The impressiones digitatæ and Pacchionian depressions were more pronounced on the left side.

On the occiput, where a trauma was sustained five years previously, no abnormal condition was observed.

The *pia* is moderately congested, and over the whole convexity is considerably thickened and opaque. The *brain* tissues appear normal. The thickness of the *parietal bones* varies greatly, especially along the sagittal suture.

Microscopical examination. The liver shows the usual lesions of advanced chronic congestion, with complete atrophy of cells at the centres of lobules, and slight fatty degeneration of cells at the peripheries of lobules.

The small nodules above described prove to be miliary adenomata. They are composed of thick cords of hypertrophic liver cells, usually containing more than one nucleus, and at some points showing considerable fatty infiltration. The larger adenomata are surrounded by a distinct fibrous capsule, within which effects of chronic congestion have not been felt, as the capillaries of the adenomata are not at all widened.[1] The cords of liver-cells surrounding the nodules are much compressed for a considerable distance. (See drawing.)

[1] In this respect our specimen differs from the majority of the few cases which have been described. In them the liver-cells were thoroughly compressed and destroyed by copious interstitial tissue, and new cells were developed through a compensatory process.

The lesions in the *lymph nodes* include:

1. A chronic inflammatory hyperplasia, with the production of new connective tissue, extensive exfoliation of endothelial cells, and atrophy of lymphoid cells.

2. An extreme dilatation of veins and capillaries, both within and without the nodes.

The inflammatory process has replaced considerable portions of the nodes by a tissue apparently composed of flattened and fusiform endothelial or connective cells, and entirely lacking in lymphoid cells. In these areas the capillaries are often dilated and gorged with blood. The lymph nodules are all quite small, and many appear to have been replaced by the above tissue. There is a slight deposit of anthracotic pigment in the fibrous tissue. The large neighboring veins are enormously dilated, and possibly increased in number so as to give an appearance not unlike that of a cavernous angioma. The venous stasis has likewise affected the vessels within the nodes, the medullary lymph cords being entirely absent and replaced by dilated blood-spaces or fibrous tissue. The condition of the lymph nodes indicates a process of older date than that of the changes in the liver.

The *mesentery* shows œdematous infiltration, and about some small vessels are collections of mononuclear and polynuclear cells.

The *spleen* shows the effects of chronic congestion equally marked with those of the liver. The sinuses are much dilated, and the pulp-cells contain a large deposit of blood-pigment.

The *intestinal wall* shows a light coating of fibrin with exfoliation of endothelial cells.

The *ovaries and Fallopian tubes* show venous congestion, but no other lesion.

Brain. The motor cortex of both sides was cut in thin slices and hardened in saturated watery solution of corrosive sublimate.

Sections stained by Nissl's method gave very unsatisfactory results, owing to advanced post-mortem changes. As nearly as could be judged, the motor areas of both sides were identical in appearances, including the numbers and configuration of the cells, and the character of chromaphilic bodies, and intracellular network. The pia of both sides was considerably thickened, that over the left motor area very much so.

Some capillaries were found containing colonies of cocci.

The ganglion cells of the cranial nerve nuclei (XII., X., IX., examined) showed no unusual appearances by Nissl's stain.

BACTERIOLOGICAL EXAMINATION. A portion of one of the superficial adenomata, including a section of the capsule of the liver, was inserted beneath the skin of a guinea-pig. Seven weeks later no inflammatory changes were to be found at the point of inoculation or in the adjoining lymph nodes.

A similar negative result followed the inoculation of another guinea-pig with a swab from the fluid and pus in the bottom of the drainage-tube. The fluid in the drainage-tube, smeared on cover-glasses, showed the presence of

numerous cocci in masses and short chains. Pure cultures of *staphylococcus pyogenes aureus* and of *streptococcus pyogenes*, of marked virulence, were secured by Dr. Charles Norris from this same fluid.

The fluid from the drainage-tube and sections of the intestinal wall, mesentery, liver, spleen, and lymph nodes were stained for tubercle bacilli, with a negative result.

The serosa of the inflamed intestines contained cocci in moderate numbers.

The spleen contained large numbers of minute colonies of cocci, and in the motor cerebral cortex and in a lymph node single colonies of cocci were observed.

DIAGNOSIS. Chronic inflammatory hyperplasia of periportal and perihepatic lymph-nodes, of undetermined origin.

Partial compression of hepatic and portal veins.

Chronic congestion of liver and portal viscera. Multiple miliary adenomata of liver.

Ascites.

Peritonitis. Tubercle bacilli in the fluid.

Septicæmia.

EPICRITICAL. From the pathological standpoint the obscure feature of the case is the relation of the swelling of the perihepatic lymph-nodes and the condition of the liver. In the absence of any other adequate cause it is necessary to conclude that the advanced chronic congestion of the liver was due to a compression of the hepatic vein from the enlarged lymph-node lying above and upon this vein. It then becomes necessary to discover a cause of this hyperplasia of the lymph-nodes, which, with the periportal nodes, were the only ones in the body thus affected. Several possibilities may be suggested. It is possible that the lymph-nodes were subjected to chronic irritation from intestinal toxæmia, in which case it is difficult to see how the mesenteric nodes could have escaped, as they did, a similar irritation and hyperplasia. The probability of a serious retrograde irritation from the thoracic chains must be regarded with caution, since the thoracic nodes were not enlarged, and the bronchial nodes showed only moderate pigmentation. The deposit of pigment in the perihepatic node was very slight and apparently quite insufficient to induce the lesion found in the node. Nevertheless such a possibility may be entertained.

Cholecystitis could have affected the periportal nodes, and suppurative lesions in this viscus commonly do so; but there were no

evidences, either gross or microscopical, of any disease of the gall-bladder. The considerable size of some of the adenomata ($\frac{1}{2}$ cm. in diameter) suggests that these may have been the primary lesions, and that the disordered condition of the hepatic circulation and function led to the hyperplasia of the lymph-nodes draining the organ. While there is no positive evidence on which to deny such a course of events, many recent studies of nodular hyperplasia of the liver tend to show that this lesion usually represents a regenerative tendency, well marked in liver-cells, to replace disordered or destroyed hepatic tissue by way of compensation. No other cause for liver congestion can be found in our case in heart, pleura, or lungs. Some extensive studies of this character have been contributed, as follows:

Flock, Ueber Hypertrophie und Neubildung der Lebersubstanz. *Deut. Arch. f. klin. Med.*, 1895, Bd. lv.

Marchand, Ueber Ausgang der acuten Leberatrophie in multiple knotige Hyperplasie. Ziegler's *Bact.*, 1895, Bd. xvii. p. 206.

Meder, Ueber acute Leberatrophie mit besonderer Berücksichtigung der dabei beobachteten Regenerationserscheinungen. Ziegler's *Beit.*, 1895, Bd. xvii. p. 143.

Therese, Des adenomes du foie. *L'Union Médicale*, 1895, No. 34.

Babes et Manicatide, Les proliferations des cellules hépatiques dans les differents affections du foie. *Ref. Cent. f. Path.*, etc., 1896, No. 23.

The very general distribution of the nodules in the present case, and the fact that they represented areas of apparently normal liver-cells—in the drawing (p. 500) the presence and absence of these cells in adjoining territory are beautifully represented—in which the effects of the chronic congestion were not at all noticeable seem to support strongly the view that these miliary adenomata were entirely the result of the advanced chronic congestion and atrophy of liver-cells which affected the entire organ.

As already stated, moreover, the lesion in the lymph-nodes appears to have been probably of older date than the adenomata of the liver.

Pressure on the hepatic vein having been once established, thereby obstructing the venous return from the nodes themselves, it is readily seen how the course of events should lead to exactly the condition found at autopsy.

The peritonitis and septicæmia which terminated the case may

properly be regarded as the natural and very frequent result of the sudden relief of pressure from the abdominal viscera, especially the intestines, allowing the passage of intestinal bacteria into the peritoneum and apparently, also, into the general circulation. The intestinal lumen contained a very abundant growth of cocci; the streptococcus and staphylococcus were isolated from the peritoneum, and bacterial thrombi composed of cocci were found in the spleen abundantly, and in the brain and lymph-nodes.

This consideration affords also a clue to the presence of tubercle bacilli in the serum contained in the abdominal cavity. They are transferred through the circulation, either of the blood or the lymph. The latter would start from lymph-nodes which were, however, nowhere affected, nor was there any organ or tissue infected with tuberculosis. Therefore the presence of tubercle bacilli can be explained by transmission through the blood-current only. Evidently they were only a complication, an incident. When the rapid effusion took place from the bloodvessels of the peritoneum and the intestine, where the bacilli happened to be located, without having given rise to local or general symptoms, the vessels were emptied of a thin serum—of 1011 specific gravity—with all its contents. The alkaline fluid in the abdominal cavity proved an excellent nutrient and a preservative for the bacilli.

The presence of bacilli in the ascitic fluid, in the absence as well of tuberculous deposits or degenerations anywhere, as of lesions in the intestine which could be charged with admitting the microbes into the circulation, is no longer an improbability, since it has been proven that surface lesions of a mucous membrane are not required to admit tubercle bacilli nor hiatuses in the epithelial covering, such as are possessed by the tonsils (Stoehr) in their normal state. It has been known for some time that initial lesions in the lungs, for instance, need not correspond with the localities of original affections, for pulmonary infiltrations will follow the subcutaneous injections of bacilli in distant places. Koch proved that lymph-bodies may become diseased without affections of their roots. Solid particles are swept through the lungs. The spores of saprophytes and of anthrax are so admitted. Whether this happens more readily in children, whose organs are less altered by the solid results of previous morbid processes, remains to be seen. Bollinger

and Heller demonstrated that tubercle virus may penetrate through intact tissue, and that we need not assume with Babes that cocci prepared the soil for absorption in every instance. The tubercle bacilli in the ascites of our case can, therefore, be explained in one of two ways. They were, before entering the abdominal cavity, contained either in the circulating blood or in the intestinal tract. The former is very improbable, for there were no miliary deposits anywhere. The presence of bacilli in the intestinal tract is explained by the facility of their admission with food. It is probable there are but few intestinal tracts but are harboring bacilli now and then. It is under favorable circumstances only that they are absorbed instead of being expelled. Such favorable circumstances are either the presence of local lesions or sudden changes of osmosis. The latter existed in our case.

The local cranial defects remain unexplained. If they had been found in the skull of a baby less than six or ten months old, they would certainly have been claimed as rhachitical. Craniotabes, however, after rhachitis gets well, seldom leaves behind any of these attenuated circumscribed spots. There was no symptom of rhachitis in the patient when an infant, except constipation. There was, moreover, no tumor, no thickening inside to explain a local absorption of such circumscribed character. I prefer to point to this instance of defective local bone development on some other than rhachitical basis.

It has been noticed that the pia and surface of the brain exhibited marked alterations from the normal, but none so circumscribed as to explain the localized spasmodic symptoms constituting the very picture of what we mean by the term Jacksonian epilepsy. The advisability of an operation undertaken to find and remove its local cause was often considered by the medical men who studied the case. It never was urged by anyone; it was advised against by some. Nothing that is positive can be learned from this feature of the case, except the necessity of care and caution and prudence.

A therapeutical remark will not be out of place. It has been seen that the bromides were sometimes required in such quantities as to interfere seriously with the general health of the patient.

When the doses of urethan recommended by Dr. Dana were given persistently the convulsive attacks ceased very soon, never to return, and there were no disagreeable symptoms attributable to the remedy.

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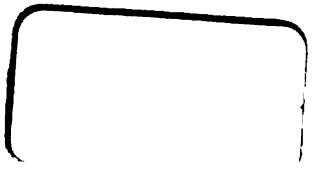
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